UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation This Document Relates To: *All Cases*	Docket No.: 22-md-3043 (DLC)

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERTS' OPINIONS REGARDING AUTISM SPECTRUM DISORDER

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Autism Spectrum Disorder ("ASD")[1] has one known cause: genetics. Scientists believe that 80-90 percent of ASD diagnoses have a genetic etiology,[2] and although some environmental exposures have been associated with an increased risk for ASD, none has been established as causal. Indeed, courts have time and again rejected speculative theories that various prenatal or neonatal events or exposures—ranging from maternal use of antidepressant medications to childhood vaccines—allegedly lead to the development of autism.[3] Plaintiffs here have advanced yet another such claim: that use of acetaminophen[4] by pregnant mothers causes ASD in their children. To that end, plaintiffs have designated five experts who seek to offer opinions that directly contradict the views of the regulatory, medical and scientific communities.

Two of plaintiffs' experts—Dr. Andrea Baccarelli and Dr. Robert Cabrera—review the epidemiological literature and offer the opinion that maternal use of acetaminophen is capable of causing ASD in children, despite a dearth of supportive epidemiologic studies and even though neither expert appears to know when during pregnancy acetaminophen supposedly causes this complex neurodevelopmental disorder ("NDD"). A third expert, psychiatrist Dr. Eric Hollander, primarily opines that a so-called "transdiagnostic" approach to NDDs supports the conclusion

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[1] A glossary of scientific terms used in defendants' three Daubert motions is attached to the Declaration of Kristen L. Richer as Ex. 171 to assist the Court in its review of Defendants' motions. Defendants' other two *Daubert* briefs are also incorporated herein.

[2] *See* Taylor, *Etiology of Autism Spectrum Disorders and Autistic Traits Over Time*, 77(9) JAMA Psychiatry 936 (2020). Copies of all studies cited herein are attached to the Declaration of Kristen L. Richer as Exs. 24-169.

[3] *See, e.g.*, *Daniels-Feasel v. Forest Pharms., Inc.*, No. 22-146, 2023 U.S. App. LEXIS 19448 (2d Cir. July 28, 2023) (antidepressant); *Hendrix v. Evenflo Co.*, 255 F.R.D. 568 (N.D. Fla. 2009) (neonatal car accident), *aff'd*, 609 F.3d 1183 (11th Cir. 2010); *Pugh v. Cmty. Health Sys., Inc.*, No. 20-00630, 2023 WL 3361166 (E.D. Pa. May 10, 2023) (allegedly negligent medical care during delivery); *Scottoline v. Women First, LLC*, No. N19C-08-135, 2023 Del. Super. LEXIS 101 (Del. Super. Ct. Mar. 1, 2023) (similar); *Arrieta v. Hosp. Del Maestro*, No. 15-3114, 2018 U.S. Dist. LEXIS 117328 (D.P.R. July 13, 2018) (similar); *Doe v. Ortho-Clinical Diagnostics, Inc.*, 440 F. Supp. 2d 465 (M.D.N.C. 2006) (thimerosal in biologic product RhoGAM); *Redfoot v. B.F. Ascher & Co.*, No. 05-2045, 2007 WL 1593239 (N.D. Cal. June 1, 2007) (thimerosal in nasal mist product); *Melnick v. Consol. Edison, Inc.*, 959 N.Y.S.2d 609 (N.Y. Sup. Ct. 2013) (slip and fall during pregnancy).

[4] The terms acetaminophen, paracetamol and APAP refer to the same active ingredient.

that acetaminophen causes ASD and attention deficit hyperactivity disorder ("ADHD"), even though he expressly acknowledges that the two disorders are "heterogeneous" and distinct. A fourth expert, pharmacologist Dr. Stan Louie, claims that prenatal exposure to acetaminophen for at least 28 days increases the risk of ASD, without any real basis in the science for that arbitrary threshold. And toxicologist Dr. Brandon Pearson offers the opinion that animal behavior studies support plaintiffs' theories, even though rodents and other animals used in such experiments have different brains from humans, cannot communicate the way humans do, and cannot be diagnosed with ASD.

Plaintiffs recently asked the U.S. Attorney for the Southern District of New York to review their experts' reports, along with a 21-page letter summarizing their experts' positions on general causation, all in an effort to persuade the U.S. Food and Drug Administration ("FDA") to buy into plaintiffs' litigation theory. That effort failed. Instead, the U.S. Attorney reiterated the FDA's Spring 2023 conclusion that "the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are ***unable*** to support a determination of causality."[5] The FDA's conclusion mirrors the reasoned judgment of numerous regulatory and public health organizations, including the American College of Obstetricians and Gynecologists ("ACOG"), the Society for Maternal-Fetal Medicine ("SMFM") and the Society of Obstetricians and Gynaecologists of Canada ("SOGC").

Plaintiffs' experts' contrary opinions are methodologically unsound and should be excluded under *Daubert* and Rule 702 for several reasons.

First, the minimal epidemiologic evidence does not support a causal inference. There are just four epidemiological studies that evaluate a potential association between maternal use of

[5] *See* Dkt. No. 1105 at 1-2 ("FDA Letter") (emphasis added).

acetaminophen and a diagnosis of ASD. One additional study has evaluated the relationship in the context of febrile women only. Three of these five studies (Ji 2018, Saunders 2019 and Hornig 2018) found ***no*** statistically significant association; one found a weak association between acetaminophen and ASD, though when broken down to subtypes, the association only remained for ASD with hyperkinetic disorder ("HKD") and not other subtypes of ASD (Liew 2016); and the one on which plaintiffs' experts principally rely found a modest association between acetaminophen in umbilical cord blood (i.e., acetaminophen taken immediately before labor and delivery) and ASD (Ji 2020). As the FDA recently concluded, this body of science is too meager and limited to support a reliable causation opinion.

Second, plaintiffs' experts also rely on studies that evaluated a potential association between maternal use of acetaminophen and the results of various screening tests (rather than a clinical diagnosis of ASD). While some of these screening tests are used as a first step in an autism evaluation, they are designed to be over-inclusive in order to ensure that anyone potentially at risk for ASD is identified; as a result, they sweep in many individuals who do not have ASD and cannot demonstrate causation.

Third, plaintiffs' experts (led by Dr. Hollander) attempt to overcome the paucity of supportive science by opining that ASD, ADHD and various other NDDs share a sufficient degree of symptomology and brain morphology such that one may infer they share the same etiology. But Dr. Hollander's so-called "transdiagnostic approach" to causation—which not only conflates ASD with ADHD, but effectively treats all NDDs as one and the same—has no scientific support.

Fourth, Drs. Baccarelli, Cabrera and Hollander also purport to apply the Bradford Hill framework as support for their general causation opinions, but that framework presupposes that

the experts have reliably identified a "clear cut" association between acetaminophen use and ASD diagnoses. They have not. And even if they had, their results-driven methodologies and analyses misread and misapply the Hill criteria. There is no strong or consistent association, the studies do not show a dose response, plaintiffs' experts concede there is no specificity in their theories, and their theories are incoherent with what is known about ASD trends.

Fifth, Drs. Pearson and Cabrera's reliance on animal studies does not fill the void that exists in the epidemiological literature. Many of the outcomes measured by the animal studies—e.g., sexual behavior in rats—are not even tangentially relevant to an ASD diagnosis in humans. And even studies that attempt to measure social behaviors are, at most, hypothesis-generating, because "[a]nimals cannot even be diagnosed with autism in the same way humans can" and "are not communicative in the way . . . humans are." *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17 CV 4188-LTS-JLC, 2021 WL 4037820, at *16 (S.D.N.Y. Sept. 3, 2021) (citation omitted), *aff'd*, No. 22-146, 2023 U.S. App. LEXIS 19448 (2d Cir. July 28, 2023). Moreover, Drs. Pearson and Cabrera selectively highlight behavioral outcomes that support their opinions, while downplaying or ignoring contrary findings, further invalidating their opinions.

Sixth, certain of plaintiffs' experts' opinions fail for a variety of other reasons. Dr. Baccarelli purports to follow a "Navigation Guide" "methodology" utilized by regulators, which is unreliable for multiple reasons. For one thing, it rests on the same methodological errors as his Bradford Hill analysis and therefore fails for the same reasons. In addition, the Navigation Guide is a regulatory standard that errs on the side of caution and may be satisfied without proof of causation—making it an improper methodology for deciding causation, even if followed properly. Dr. Baccarelli's opinions in this litigation also directly conflict with statements he made in published literature before he was retained by plaintiffs' counsel—e.g., Laue 2019 and

Baker 2022—strongly suggesting that the conclusions in his report were manufactured for purposes of this litigation. And Dr. Louie's opinion that exposure to acetaminophen for at least 28 cumulative days increases the risk of developing both ASD and ADHD is essentially plucked from the air and lacks any scientific basis.

In short, plaintiffs' experts' general causation opinions are an exercise in scientific overreach that has been rejected by the FDA and has no place in court. Rule 702 imposes a gatekeeping function to prevent precisely what plaintiffs' experts seek to do here: i.e., to misinterpret the relevant literature and misapply scientific methods in the hopes of persuading jurors that cherry-picked results support causation. Such fundamental failures go to admissibility; they are not questions of "weight" that should be decided by lay jurors. *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 284 (4th Cir. 2021). "The courtroom is not the place for scientific guesswork . . . . Law lags behind science; it does not lead it." *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 270-71 (S.D.N.Y. 2018) ("*Mirena II*") (citation omitted), *aff'd*, 982 F.3d 113 (2d Cir. 2020). For these reasons, discussed in more detail below, plaintiffs' experts' ASD opinions should be excluded under *Daubert*.

BACKGROUND

A. Acetaminophen

Acetaminophen, an analgesic and antipyretic agent, has been considered safe and effective for treatment of pain and fever for over half a century. Acetaminophen is unique among pain and fever treatments because it is considered by the FDA and the medical community to be safe for use during pregnancy.[6] The availability of acetaminophen to pregnant women is

[6] *See* FDA, *FDA Recommends Avoiding Use Of NSAIDs in Pregnancy at 20 Weeks or Later Because They Can Result in Low Amniotic Fluid* (Oct. 15, 2020), https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic ("Other

important because "[s]evere and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure."[7] The FDA requires labels for over-the-counter ("OTC") medications "intended for systemic absorption," including acetaminophen, to state—with the first four words in bold type—"**If pregnant or breast-feeding**, ask a health professional before use." 21 C.F.R. § 201.63(a); FDA, *Pregnant or Nursing Women*, 47 Fed. Reg. 54,750 (Dec. 3, 1982). In imposing this requirement, the FDA explained that "a woman would be best advised on whether to use a particular OTC drug by a knowledgeable health professional who is either familiar with her medical history or readily available to her and capable of assessing her situation with respect to a particular drug." 47 Fed. Reg. at 54,751.

B. Autism Spectrum Disorder

ASD is a "complex developmental condition involving persistent challenges with social communication, restricted interests, and repetitive behavior."[8] As set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition ("DSM-5"), a clinical diagnosis of ASD requires a finding by a clinician that a child has "[p]ersistent deficits" in: (1) social-emotional reciprocity; (2) nonverbal communicative behaviors; and (3) developing, maintaining, and understanding relationships.[9] Diagnosis also requires proof of two of the following four restricted, repetitive behaviors: (1) stereotyped or repetitive motion or movements; (2) insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior; (3) highly

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medicines, such as acetaminophen, are available to treat pain and fever during pregnancy.").

[7] FDA, *Drug Safety Communication: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy* (Jan. 9, 2015), https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy.

[8] American Psychiatric Association, *What Is Autism Spectrum Disorder?*, https://www.psychiatry.org/patients-families/autism/what-is-autism-spectrum-disorder#section_3 (last visited Sept. 7, 2023).

[9] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), at 50.

restricted and abnormal fixated interest; and (4) hyper- or hypo- reactivity to sensory input.[10]

Studies have shown that the heritability of ASD is as high as 80-90%, and certain variants of ASD like Fragile X or Rett syndrome are entirely caused by single gene mutations. (*See* Rep. of Alexander Kolevzon at 15, July 21, 2023 (Ex. 1).) Notably, sibling control studies (in which the investigated exposure occurred only during one sibling's pregnancy)[11] have found that proposed associations between labor induction, antidepressants, smoking, c-section and maternal infection and ASD were attenuated to the null once genetic confounding was addressed.[12]

The only exposure that is accepted as a risk factor for ASD is maternal use of valproic acid (an anti-seizure medication), which has been found in some studies to increase the risk of ASD by 300%.[13] Because valproic acid (in contrast to acetaminophen) is a prescribed medication that is only indicated for specifically diagnosed disorders, data on dosages and durations (as well as trimester of use) can be precisely gleaned from medical records. Nonetheless, scientists have not concluded that the association is causal.

C. Fundamental Epidemiologic Principles

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10 *See id.*

11 Sjölander, *Sibling Comparison Studies*, 9 Annu. Rev. Stat. Appl. 71 (2022).

12 Oberg, *Association of Labor Induction With Offspring Risk of Autism Spectrum Disorders*, 170(9) JAMA Pediatrics 1 (2016) ("Oberg 2016"); Yang, *Risk of Autism Spectrum Disorder in Offspring Following Paternal Use of Selective Serotonin Reuptake Inhibitors Before Conception: A Population-Based Cohort Study*, 7 BMJ Open 1 (2017); Kalkbrenner, *Familial Confounding of the Association Between Maternal Smoking in Pregnancy and Autism Spectrum Disorder in Offspring*, 13(1) Autism Research 134 (2020); Zhang, *Assessment of Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders in the Children of a Population-Based Swedish Birth Cohort*, 4(3) JAMA Network Open 1 (2021); Curran, *Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study*, 72(9) JAMA Psychiatry 935 (2015) ("Curran 2015"); Brynge, *Maternal Infection During Pregnancy and Likelihood of Autism and Intellectual Disability in Children in Sweden: A Negative Control and Sibling Comparison Cohort Study*, 9 Lancet Psychiatry 782 (2022); Hegvik, *Labor Epidural Analgesia and Subsequent Risk of Offspring Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder: A Cross-National Cohort Study of 4.5 Million Individuals and Their Siblings*, 228 Am. J. Obstet. Gynecol. 233.e1 (2023); Ren, *Association of Labour Epidural Analgesia With Neurodevelopmental Disorders in Offspring: A Danish Population-Based Cohort Study*, 128(3) British J. Anaesthesia 513 (2022).

13 *See* Christensen, *Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism*, 309(16) JAMA 1696 (2013).

Epidemiologic studies measure the occurrence of a condition in groups of "individuals who have been both exposed and unexposed to the putative risk factor." *Daniels-Feasel*, 2021 WL 4037820, at *2 (citation omitted). Epidemiological studies generally report their results in terms of relative risks ("RR") and odds ratios ("OR")[14] (sometimes referred to as hazard ratios ("HR")). *Id.* For purposes of evaluating general causation, these are essentially interchangeable concepts that describe the increase (or decrease) in risk between exposure and disease. For example, a relative risk of 1.0 means that the disease was found to occur no more frequently than in the general population.[15] A relative risk of 2.0 means that the disease was found to occur twice as frequently (a 100% increased risk), and a relative risk of 0.5 means the disease was found to occur half as frequently (representing a 50% decrease in risk). *See id.*; *see also Daniels-Feasel*, 2021 WL 4037820, at *2.

"Where a positive association is observed, its validity is assessed by evaluating the role of possible alternative explanations, such as chance, bias, or confounding." *Daniels-Feasel*, 2021 WL 4037820, at *2. "Chance, or random error, is typically evaluated through measures of 'statistical significance,' which is usually reported using a range of values referred to as the '95% confidence interval' ('CI')." *Id.* (citing *RMSE*, at 247, 579-80). A confidence interval provides 95% certainty of the true risk estimate. *Id.* If a confidence interval includes 1.0 (i.e., the possibility of no association), it cannot be said with 95 percent confidence that there is any association between the exposure and the outcome, and the finding is considered to be "not statistically significant." *Id.* A related concept is "p-value." A p-value provides a probability that there is no association between exposure and outcome (known as the "null hypothesis"). A

[14] An adjusted odds ratio ("aOR") adjusts for known confounders.

[15] *Reference Manual on Scientific Evidence* ("*RMSE*") (3d ed. 2011), at 574.

p-value less than 0.05 is generally considered to support an association in a study (although in some instances a lower p-value is required), while a p-value above 0.05 (or as otherwise specified) would be considered not statistically significant and not supportive of an association.[16]

"Bias is a systematic, non-random error, that may appear, for example, in the case of information bias, where the available records for one group are more likely to include relevant information than another." *Daniels-Feasel*, 2021 WL 4037820, at *3 (citing *RMSE*, at 249). Misclassification bias occurs when there are errors in reporting with respect to both exposure and outcome. Confounding refers to "[a] factor that is both a risk factor for the disease and a factor associated with the exposure of interest." *Id.* (citation omitted). "[C]onfounding by indication refers to a factor that is associated both with the indication for the prescription and with the outcome of interest." *Id.* (citation omitted).

D. The Scientific, Medical And Regulatory Communities Have Rejected A Causal Relationship Between Acetaminophen And ASD.

1. The Relevant Scientific Literature Is Sparse And Inconsistent.

Only five epidemiological studies have assessed the association between maternal exposure to acetaminophen and clinical diagnoses of ASD in children, and three found ***no*** association or a ***negative*** association (i.e., that acetaminophen has a ***protective*** effect):

Ji 2018.[17] This study followed 1,180 infants from the Boston Birth Cohort using maternal blood samples taken 1-3 days post-partum. The authors used maternal plasma biomarkers to eliminate recall bias (i.e., inaccurate recall of medication use during pregnancy).

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[16] *See RMSE*, at 576-77 ("[A]n outcome is statistically significant when the observed *p*-value for the study falls below the preselected significance level. The most common significance level, or alpha, used in science is .05.").

[17] Ji, *Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder*, 8(127) Brain Sci. 1 (2018) ("Ji 2018").

Specifically, maternal blood was sampled for three different particles (unchanged acetaminophen and its metabolite byproducts acetaminophen glucuronide and 3-(*N*-Acetyl-L-cystein-*S*-yl) acetaminophen) to estimate the total amount of acetaminophen present near the time of delivery.[18] The authors calculated a total "acetaminophen burden" "by combining all of the acetaminophen metabolites levels with a weighting of their proportions in the acetaminophen metabolic pathway."[19] Because acetaminophen has a 2-3 hour half-life in adults, detectable levels of acetaminophen would have reflected "recent use"—i.e., at or near labor. The authors calculated 48 odds ratios and confidence intervals based on different estimation models and different acetaminophen proxies (unchanged, metabolites, total burden), but not a single analysis yielded a statistically significant association between acetaminophen exposure and ASD.[20]

Saunders 2019.[21] This study used a case-control design to explore the relationship between various environmental exposures, including medication use, and ASD. The ASD group consisted of 141 children, 10 and under, who were diagnosed with ASD before age 6 and had no other developmental disorder or chromosomal abnormality.[22] The control group consisted of 199 age- and sex-matched children without ASD from the "same region" of the same city in Atlantic Canada.[23] The authors asked both groups of mothers about various environmental exposures

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[18] As acetaminophen is metabolized by the body, it becomes converted into other molecules, including acetaminophen glucuronide and 3-(N-Acetyl-L-cystein-S-yl). To properly estimate the total amount of acetaminophen likely taken by the mother near the time of labor, the study authors attempted to measure both the amount of unchanged acetaminophen (not yet metabolized), as well as the two most common byproducts (the two acetaminophen metabolites). *See id.*

[19] *Id.* at 4.

[20] *Id.* at 7 ("[T]he risks of ASD diagnosis . . . were not significantly associated with maternal plasma levels of acetaminophen metabolites across all models.").

[21] Saunders, *A Comparison of Prenatal Exposures in Children With and Without a Diagnosis of Autism Spectrum Disorder*, 11(7) Cureus 1 (2019) ("Saunders 2019").

[22] *See id.* at 2.

[23] *See id.*

during pregnancy, including acetaminophen use.[24] The authors did not find an association between acetaminophen exposure and the development of ASD.

Liew 2016.[25] The authors followed 64,322 children and mothers from the Danish National Birth Cohort.[26] Maternal acetaminophen use was evaluated based on telephone interviews performed during pregnancy, while children's diagnoses were taken from the Danish National Hospital Registry and Danish Psychiatric Central Registry.[27] The results were mixed. As compared to "never use," "ever use" of acetaminophen was associated with a very small, but statistically significant, increase in ASD risk (aHR=1.19, 95% CI 1.04-1.35).[28] When those risks were broken down by subtype, however, the only one for which a statistically significant association remained was ASD with HKD (aHR=1.51, 95% CI 1.19-1.92).[29] The authors did not explain why acetaminophen would be associated with cases involving HKD, but not with other cases.[30] The Liew 2016 authors expressly acknowledged the "possibility of residual confounding by indication or genetic factors as alternate explanations" for their findings.[31]

Ji 2020.[32] Like Ji 2018, this study used a sample of 996 children from the Boston Birth

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24 *See id.* at 2-3.

25 Liew, *Maternal Use of Acetaminophen During Pregnancy and Risk of Autism Spectrum Disorders in Childhood: A Danish National Birth Cohort Study*, 9 Autism Research 951 (2016) ("Liew 2016").

26 *See id.* at 952.

27 *See id.*

28 *See id.* at 955 (Table 2).

29 *See id.* (Table 3).

30 *See id.* at 954 ("[W]e find that fetal exposure to acetaminophen affects ASD with hyperkinetic, but not ASD without hyperactivity features. If ASD and hyperkinetic disorder are considered two different disorders with different etiologies, our results can be interpreted as acetaminophen only having an impact on hyperkinetic disorder but not ASD.").

31 *See* Liew 2016, *supra* note 25, at 956.

32 Ji, *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood*, 77(2) JAMA Psychiatry 180 (2020) ("Ji 2020").

Cohort and investigated a possible association between acetaminophen biomarkers (this time maternal blood and umbilical cord blood) and ASD and other NDDs. The mothers' total acetaminophen burden was divided into thirds ("tertiles"). The third tertile of cord blood measurements for acetaminophen had an elevated risk of ASD without ADHD (aOR=3.62, 95% CI 1.62-8.60), but there was no statistically significant risk of ASD with ADHD (aOR=2.44, 95% CI 0.92-6.82). The second tertile had no statistically significant risk for either.[33] Oddly, the authors found that "all cord samples had detectable unchanged acetaminophen,"[34] suggesting that women were exposed to background acetaminophen or that there was laboratory error in the cord blood measurements. (*See* Am. Rep. of Andrea Baccarelli ("Baccarelli Am. Rep.") at 102, June 23, 2023 (Ex. 2).) While the Ji 2020 results were adjusted for certain environmental exposures, they did not control for parental or genetic risk factors.[35]

Hornig 2018.[36] This study did not directly measure the association between maternal use of acetaminophen and childhood ASD, but it did evaluate whether maternal fever increased the risk of ASD in children and whether acetaminophen mitigated that risk. The study found that maternal fever was associated with a slightly increased risk of ASD across all trimesters (aOR=1.34, 95% CI 1.07-1.67), and the authors reported a dose-response relationship with three or more fevers after 12 weeks of pregnancy (aOR=3.12, 95% CI 1.28-7.63).[37] According to the authors, "[r]isk tended to be lower within each trimester in febrile women who took

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33 *Id.* at 186.

34 *Id.*

35 *Id.* at 188 ("[W]e were unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors.").

36 Hornig, *Prenatal Fever and Autism Risk*, 23 Molecular Psychiatry 759 (2018) ("Hornig 2018").

37 *Id.* at 762, 764.

acetaminophen for fever than in febrile women who did not," suggesting a protective effect.[38] Indeed, in the second trimester, acetaminophen treatment reduced the risk of ASD associated with fever to a non-significant level (untreated fever aOR=1.44, 95% CI 1.02-2.03; fever treated with acetaminophen aOR=1.37, 95% CI 0.98-1.90).[39] Notably, "none of the women with [children] later diagnosed with ASD used ibuprofen for fever in pregnancy," suggesting that ibuprofen did *not* reduce the risk of ASD associated with fever.[40]

2. Objective Scientific Reviews By Governmental And Public Health Agencies Reject A Causal Relationship.

Despite more than a decade of intense scrutiny, major regulatory agencies and scientific institutions have determined that there is insufficient scientific evidence to conclude that maternal use of acetaminophen during pregnancy causes ASD in children.

FDA. "Between 2014 and 202[3], the [FDA's] Division of Epidemiology I (DEPI-I) conducted [six] literature reviews on in utero APAP exposure and neurobehavioral . . . outcomes."[41] In 2015, the FDA released a Drug Safety Communication concluding that the available evidence on the proposed relationship between acetaminophen and ASD was "too limited to make any recommendations" and did not warrant any change to the agency's "recommendations on how pain medicines are used during pregnancy."[42] Subsequent

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38 *Id.* at 762.

39 *Id.* at Supplementary Table S6.

40 *Id.* at 763. The authors cautioned that, due to small sample sizes, definitive conclusions about ibuprofen's fever-modification effects could not be drawn.

41 *See* Dkt. No. 1105-1 (emphasis added) (citation omitted) ("FDA 2023 Review"); *see also* FDA Letter, at 1-2 ("Since 2014, FDA has conducted multiple reviews of relevant epidemiological data concerning prenatal exposure to acetaminophen.").

42 FDA, *FDA Drug Safety Communication: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy* (Jan. 9, 2015), https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy.

evaluations in 2016, 2017 and 2018 reaffirmed that higher quality data were needed to justify changes in acetaminophen labels.[43] In 2022, the FDA again stated that "the limitations and inconsistent findings of current observational studies of APAP and neurobehavioral . . . outcomes are unable to support a determination of causality."[44] And in March 2023, the FDA completed yet another review, concluding that "the new 'studies reviewed here are limited and do not change [the agency's] conclusions from its most recent review—the limitations and inconsistent findings of current observational studies of [acetaminophen] and neurobehavioral . . . outcomes are unable to support a determination of causality.'"[45] In particular, the FDA stressed that the "clinical significance of" purported associations between acetaminophen use and certain behavioral symptoms is "unclear," and that the studies are "limited by their one-time assessments of APAP exposure and their lack of adjustment for key confounders, namely indications like fever and headache/migraine."[46]

ACOG. ACOG is the "premier professional membership organization" for OBGYN physicians.[47] In September 2021, after examining the available scientific literature, ACOG found that the "studies that have been conducted in the past[] show no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues."[48] Accordingly, ACOG reaffirmed that "physicians should not change

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43 *See* Dkt. No. 483-1 at FDACDER000049-FDACDER000056, FDACDER000077-78; Dkt. No. 468-1 at FDACDER000261-271.

44 Dkt. No. 483-1 at FDACDER000082-85.

45 FDA Letter (quoting Ex. A to Letter).

46 FDA 2023 Review, at 3.

47 *See* ACOG, *About Us*, https://www.acog.org/about (last visited Sept. 7, 2023).

48 *See* ACOG, *ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy* (Sept. 29, 2021), https://www.acog.org/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy.

clinical practice until definitive prospective research is done,"[49] and that "acetaminophen [is] one of the only safe pain relievers for pregnant individuals during pregnancy."[50] Accordingly, ACOG's clinical guidelines continue to "strong[ly] recommend[]" use of "1,000 mg [of APAP] orally as initial therapy for the treatment of acute migraine" during pregnancy[51] and to recommend "acetaminophen for treatment of fever."[52] ACOG also reiterated that other analgesics (e.g., ibuprofen) should ***not*** be used during pregnancy and may lead to fetal injury.[53]

SMFM. The SMFM is a professional organization for obstetricians dealing with high-risk pregnancies and maternal-fetal medicine.[54] In March 2017, after examining the literature on acetaminophen and neurodevelopmental outcomes, the SMFM found serious deficiencies in the available studies due to self-reported exposure metrics (recall bias) in some studies, "no information on dosage and duration" in others, and weak or no associations.[55] Based on this evaluation, the SMFM "believe[s] that the weight of evidence is inconclusive regarding a

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49 *See id.*

50 *See id.*

51 ACOG, *Clinical Practice Guideline No. 3: Headaches in Pregnancy and Postpartum*, 139(5) Obstetrics & Gynecology 944, 945 (2022) ("ACOG *Clinical Practice Guideline No. 3*").

52 ACOG, *Committee Opinion No. 753: Assessment and Treatment of Pregnant Women With Suspected or Confirmed Influenza*, 132(4) Obstetrics & Gynecology e169 (2018) (reaffirmed 2021).

53 *See* ACOG *Clinical Practice Guideline No. 3*, *supra* note 51, at 958-59. One of plaintiffs' experts, Dr Baccarelli, heavily criticizes ACOG, which he claims "offer[s] no evidence" and has not studied the issue closely despite continuing to recommend maternal use of acetaminophen. *See* Dep. of Andrea Baccarelli ("Baccarelli Dep.") 119:20-120:5, 142:11-24, Aug. 14, 2023 (Ex. 3). But ACOG re-released practice guidelines just a year ago, reaffirming its commitment to acetaminophen as a therapeutic tool for pregnant women after undertaking an extensive, systematic review of available scientific literature. *See* ACOG *Clinical Practice Guideline No. 3*, *supra* note 51. Methods included "a comprehensive literature search for primary literature within Cochrane Library . . . EMBASE, PubMed, and MEDLINE," as well as a "full-text screening stage" where studies "were assessed by two authors from the writing team," followed by "quality assessment" and an "evidence-to-decision framework was applied to interpret and translate the evidence into recommendation statements." *See id*. at 944.

54 SMFM, *What is the Society for Maternal-Fetal Medicine?*, https://www.smfm.org/what-is-the-society (last visited Sept. 7, 2023).

55 SMFM, *SMFM Statement: Prenatal Acetaminophen Use and Outcomes in Children* (Mar. 2017), https://www.smfm.org/publications/234-smfm-statement-prenatal-acetaminophen-and-outcomes-in-children.

possible causal relationship between acetaminophen use and neurobehavioral disorders in the [children]" and that acetaminophen use during pregnancy is "reasonable and appropriate."[56]

SOGC. In 2021, SOGC, Canada's leading society for obstetricians and gynecologists, found that "evidence for causality for this claim is weak and has many fundamental flaws."[57] Accordingly, SOGC concluded that "clinical practice should not be altered and that acetaminophen should continue to be used for managing fever and/or pain in pregnancy."[58]

3. The Bauer Statement And Counterstatement.

Plaintiffs and their experts rely heavily on a so-called "consensus" statement entitled *Paracetamol Use During Pregnancy—A Call for Precautionary Action*,[59] even though the authors later clarified that they had ***not*** made "any inference of causality" with respect to ASD or ADHD and reiterated that "for fever and severe pain during pregnancy," "APAP is a necessary and appropriate treatment."[60] The authors "call[ed] for precautionary action" in the form of "a focused research effort" to better understand the limitations in the literature to date—specifically, "confounding by indication for use"; failure to "control for genetic factors"; inaccurate measures of "exposure and outcome"; and inadequate data concerning "timing, dosage and duration of exposure both prenatally and postnatally."[61] The authors also recommended that pregnant women be advised not to use acetaminophen "unless medically indicated"; to "consult with their

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56 *Id*.

57 SOGC, *Statement on the Use of Acetaminophen for Analgesia and Fever in Pregnancy* (Nov. 8, 2021), https://sogc.org/en/en/content/featured-news/Statement_on_the_use_of_acetaminophen.aspx.

58 *Id*.

59 Bauer, *Consensus Statement: Paracetamol Use During Pregnancy—A Call for Precautionary Action*, 17 Nature Revs. Endocrinology 757, 758 (2021) ("Bauer 2021").

60 Bauer, *Reply to "Paracetamol Use in Pregnancy—Caution over Causal Inference from Available Data": "Handle with Care—Interpretation, Synthesis and Dissemination of Data on Paracetamol in Pregnancy"*, 18 Nature Revs. Endocrinology 192 (2022) (endnote omitted).

61 Bauer 2021, *supra* note 59, at 759.

physician or pharmacist if they are uncertain whether use is indicated" (which is exactly what the current Pregnancy Warning advises); and to "us[e] the lowest effective APAP dose for the shortest possible time."[62] Notably, the Bauer statement generated a "consensus counterstatement" that was supported by numerous "scientists, clinicians, epidemiologists and teratology information specialists," who cautioned "against an inference of causality that is based upon inadequate evidence."[63] As these scientists explained, "the[] [relevant] studies are limited by serious methodological problems, including failure to account for confounding, and elements of bias that make interpretation of the data challenging."[64]

E. Plaintiffs' Experts' General Causation Opinions

1. Dr. Baccarelli

Dr. Baccarelli, an epidemiologist, asserts that "[s]ubstantial evidence supports a strong, positive, causal association between acetaminophen and Neurodevelopmental Disorders (NDDs)—particularly Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and their related symptoms." (Baccarelli Am. Rep. at 2.) Dr. Baccarelli claims to have conducted "an extensive review of the scientific evidence" (*id.*), which culminated in grading all studies reporting a positive association as "very strong" or "strong" and ranking any that found no such relationship as "very weak/none." (*See id.* at App. 1.)

In addition to Ji 2020 and Liew 2016, Dr. Baccarelli relies heavily on studies that used various screening tools and questionnaires to measure symptoms or behaviors purportedly associated with ASD. (*See* Baccarelli Am. Rep. at 109-12.) None of these studies evaluated

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62 *Id.*

63 Alwan, *Paracetamol Use In Pregnancy—Caution Over Causal Inference From Available Data*, 18 Nature Revs. Endocrinology 190 (2022).

64 *Id.*

children with confirmed ASD diagnoses, and some of the symptoms/behaviors measured (e.g., child IQ) are not at all indicative of ASD. Even as to behaviors that are found among children with ASD, many are also associated with multiple other conditions, such as anxiety, depression, avoidant personality disorder, or obsessive-compulsive disorder ("OCD"). (*See id.* at 43 ("poor eye contact and low social initiative are common . . . in individuals diagnosed with depression, anxiety, schizoid personality disorder, or avoidant personality disorder").)

Dr. Baccarelli evaluated the studies using a result-oriented, non-scientific method that led him to discount or disregard studies that found no statistically significant association between prenatal acetaminophen exposure and purported ASD symptoms, including Leppert 2019 and Avella-Garcia 2016, even though he touts the results from the latter study as support for his ADHD opinion. (*Compare* Baccarelli Am. Rep. at 83 (Avella-Garcia 2016 was "well designed, conducted a comprehensive assessment of confounders . . . and had rich data"), *with* Baccarelli Am. Rep. at 98 (ignoring finding of no statistically significant association as to ASD).)

Throughout his report and deposition testimony, Dr. Baccarelli downplays the role of genetics in the etiology of ASD, putting him at odds with the FDA, scientific and medical literature and even plaintiffs' other experts, such as Dr. Cabrera, who testified that as many as 80-90% of ASD cases are linked to genetic causes. At his deposition, Dr. Baccarelli testified that he "wouldn't say" that genetics "cause[s]" ASD because "genetics cause[s] almost nothing. It contribute[s] to a lot of disease[s]." (Baccarelli Dep. 238:22-239:10.) And when questioned about Ji 2020's inability to exclude potential genetic confounding factors, Dr. Baccarelli declared that "[g]enetics has absolutely nothing to do with this" (*id.* 404:13-17), in contravention of the authors' express limitation.

Dr. Baccarelli has also flip-flopped on a number of issues since being retained as a

plaintiffs' expert. For example, as a co-author of the Laue 2019 study, Dr. Baccarelli wrote that: (1) parental reporting results in bias and inaccuracies; and (2) a lack of association with lower IQ scores suggested that acetaminophen did not cause any NDDs.[65] Dr. Baccarelli vigorously defended Laue 2019 prior to being retained as an expert in this litigation, first promoting the view that there is "no association between acetaminophen levels in #meconium and child #neurodevelopment" on Twitter in January 2020[66] and then rejecting Bauer's criticism of Laue.[67] In his report for this litigation, by contrast, Dr. Baccarelli endorses parental reporting by relying on Bornehag 2018 (which examined language delay) as support for his opinions (*see* Baccarelli Am. Rep. at 107; *see also id.* at App. 1, p. 15)—i.e., the same type of assessment method Dr. Baccarelli criticized in Laue.

In another about-face, Dr. Baccarelli published an article just last year, Baker 2022, that said "more studies in a diverse range of cohorts are needed before suggesting a change in clinical practice" regarding acetaminophen use for pregnant women.[68] However, at his deposition, Dr. Baccarelli testified that he already (secretly) held the view that acetaminophen should not be used at the time Baker 2022 was published. (*See* Baccarelli Dep. 424:7-8.)

Although Dr. Baccarelli testified that he wrote his entire report himself, large portions of Dr. Baccarelli's report appear to be cut and pasted from hearing testimony authored by Dr. Anne

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65 *See* Laue, *Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study*, 167(1) Toxicol. Sci. 138, 143 (2019) ("Laue 2019") ("Whereas many previous studies have used parental report of their child's abilities, our measurement is less biased and thus improves estimation of the effect estimate."); *id.* ("In conclusion, we did not find evidence of neurodevelopmental harm from prenatal exposure to acetaminophen measured in meconium.").

66 *See* Baccarelli Dep. Ex. 94 (Jan. 2020 Twitter Thread) (Ex. 4).

67 *Id.*

68 Baker, *Association of Prenatal Acetaminophen Exposure Measured in Meconium With Adverse Birth Outcomes in a Canadian Birth Cohort*, 10 Frontiers in Pediatrics 1, 6 (2022) ("Baker 2022").

McTiernan, a plaintiffs' expert in talc litigation, addressing the proposed relationship between talcum powder and ovarian cancer.[69] Similarities between the two are set forth in Exhibit 170.

2. Dr. Cabrera

Dr. Cabrera, a biologist, opines that "[t]herapeutic dosages of acetaminophen taken by pregnant wom[e]n are sufficient to cause" ASD. (Am. Rep. of Robert Cabrera ("Cabrera Am. Rep.") at 6, June 22, 2023 (Ex. 6).) His report addresses, *inter alia*, human epidemiological studies (*see id.* at 128-68), animal behavioral studies (*see id.* at 73-95), mechanistic studies (*see id.* at 38-73), and acetaminophen toxicity studies (*see id.* at 29-31). In reaching his opinions on general causation, Dr. Cabrera says he performed a "systematic review" of the relevant literature (*see id.* at 7), used a "Weight of the Evidence" analysis for "examining study quality," and applied the Bradford Hill factors (*id.*).

Based on his review of the human observational studies assessing the proposed "[a]ssociation of APAP with ASD," Dr. Cabrera concludes that there is "some evidence" of causation, despite admitting that the "magnitude of this risk is low in the majority of studies." (*Id.* at 134, 189.) Although Dr. Cabrera acknowledges that most of the studies (e.g., Saunders 2019) reported no association, he places great weight on Ji 2020, the only study with a risk outcome above his self-identified "low" range of 1.0-2.0. (*See id.* at 189.) But even Ji 2020 only showed a "moderate" association under Dr. Cabrera's rating system; it also did not report a statistically significant increase for the second tertile of cord acetaminophen burden, and it did not adjust for potential genetic confounders. (*See id.* at 132.) Moreover, as Dr. Cabrera admitted, because Ji 2020 was based on cord blood measurements, "we don't know" anything

[69] Rep. of Anne McTiernan, M.D., Ph.D. to the House of Representatives Subcommittee on Economic and Consumer Policy (Mar. 12, 2019) (Ex. 5).

about acetaminophen usage "behaviors prior to" labor and delivery. (Dep. of Robert Cabrera ("Cabrera Dep.") 230:8-12, Aug. 2, 2023 (Ex. 7).) Accordingly, there was "no way of determining whether [the mothers] took [the] medication during the first trimester of pregnancy" (*id.* 251:5-7) or the second, which, according to him, is the most "critical" time of neurodevelopment (*see id.* 23:13-24:2).

Dr. Cabrera also relies on several studies that attempted to measure the effects of prenatal acetaminophen exposure on various neurodevelopmental symptoms, although he ignores studies finding no statistically significant association (Avella-Garcia 2016, Laue 2019, Parker 2019, Tovo-Rodrigues 2020). (*See* Cabrera Am. Rep. at 153-58.) Dr. Cabrera also cites various "meta-analyses" that he claims constitute "clear evidence" of an increased risk of ASD and ADHD (*id.* at 175), but most of those studies (Kim 2020, Patel 2022 and Ricci 2023) only pooled data regarding the risk of ADHD (*see id.* at 164-65). Indeed, Ricci noted that there was an "insufficient number of comparable studies" to complete a meta-analysis with respect to ASD.[70]

Finally, Dr. Cabrera discusses the critical need for cross-species and non-rodent behavioral studies to draw reliable conclusions in humans but never identifies a single non-rodent study evaluating ASD-like behavior or symptom domains. (*See id.* at 76, 78, 117-18.) Moreover, within the rat and mice studies he cites, Dr. Cabrera consistently omits behavioral findings of no association. And he relies on a number of irrelevant studies, such as those discussing rodent sexual behavior. (*See id.* at 85.)

3. Dr. Pearson

Dr. Pearson is a toxicologist who primarily opines that "preclinical studies strengthen the

[70] Ricci, *In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-Analysis*, 37 Paediatr. Perinat. Epidemiol. 473, 482 (2023) ("Ricci 2023").

association seen in epidemiological studies between in utero exposure to APAP and neurodevelopmental disorders including ASD." (Am. Rep. of Brandon Pearson ("Pearson Rep.") at 4, June 21, 2023 (Ex. 8).) Dr. Pearson focuses on in vivo, in vitro, and computer model studies to examine mechanistic and behavioral outcomes that he asserts relate to ASD. (*See id.* at 6.) Many of the rodent studies cited by Dr. Pearson (Blecharz-Klin 2017, Rigobello 2021) did not find a statistically significant association in key symptom domains like social or communicative behavior (*see id.* at 89, 96-97), but he takes the position that "heterogeneity of the results is not a reason to dismiss the effects of APAP" (*see id.* at 127).

4. Dr. Louie

Dr. Louie is a pharmacologist retained by plaintiffs to investigate whether and at what exposure level acetaminophen "increases the risk of developing autism spectrum disorder" and ADHD. (Am. Rep. of Stan Louie ("Louie Am. Rep.") ¶ 15, June 21, 2023 (Ex. 9).) His core opinion is that "prenatal exposure to acetaminophen in the therapeutic dose range . . . for at least 28 cumulative days during pregnancy increases the risk of ASD/ADHD development by two-fold," regardless of when during the pregnancy the mother takes the medication. (*Id.* ¶ 28; Dep. of Stan Louie ("Louie Dep.") 90:7-15, Aug. 7, 2023 (Ex. 10).) In support of that opinion, Dr. Louie relies primarily on "studies by Brandlistuen et al[.], Ystrom et al[.], and Gustavson," which he claims "all found that acetaminophen exposure beyond 28 days showed a two-fold increased risk for childhood ADHD and ASD diagnosis." (*Id.* ¶ 81.) None of those studies assessed clinical diagnoses of ASD. Brandlistuen (to which Dr. Louie "assigned the greatest weight") (Louie Am. Rep. ¶ 71) evaluated "psychomotor development," "behavior" and

"temperament,"[71] while Ystrom 2017 and Gustavson 2021 addressed ADHD diagnoses.[72] Dr. Louie also asserts that "[f]indings from the Liew studies published in 2014 and 2016, and the Vlenterie study, have results that are generally consistent with the [28-days] exposure threshold." (Louie Am. Rep. ¶ 81.) But only one of those studies—Liew 2016—looked at ASD diagnoses, and it "count[ed] total weeks of use" only (without considering how much acetaminophen was taken within each week).[73]

Although Dr. Louie alternatively opines that a cumulative dose ranging from 18,200 mg (a single 650 mg dose taken 28 times) to 112,000 mg (a maximum approved daily dosage of 4,000 mg taken on 28 days) increases the risk of developing ASD, he does not cite any scientific literature supporting that claim in his report. (*See* Louie Am. Rep. ¶¶ 26-31, 188-89; *see also* Louie Dep. 100-01.) When asked at his deposition to identify a scientific basis for this opinion, Dr. Louie pointed to two studies—Ystrom 2017 and Liew 2016 (Louie Dep. 102:22-103:10). But Ystrom 2017 involved ADHD (not ASD) and found that the use of acetaminophen for fewer than eight days was ***negatively*** associated with that condition,[74] and Liew 2016 did not report any data on total dosage.

Dr. Louie's report also touches on various "epidemiological studies" that he claims "support a causal association between prenatal exposure to therapeutic doses of acetaminophen and ASD/ADHD." (Louie Am. Rep. at 22-36 (capitalization altered).) When probed about the relevant epidemiological evidence at his deposition, however, Dr. Louie repeatedly "defer[red] to

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71 Brandlistuen, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Sibling-Controlled Cohort Study*, 42(6) Int'l J. Epidemiol. 1702 (2013) ("Brandlistuen 2013").

72 *See, e.g.*, Ystrom, *Prenatal Exposure to Acetaminophen and Risk of ADHD*, 140(5) Pediatrics 1 (2017) ("Ystrom 2017"); Gustavson, *Acetaminophen Use During Pregnancy and Offspring Attention Deficit Hyperactivity Disorder – A Longitudinal Sibling Control Study*, 1(2) JCPP Advances 1 (2021) ("Gustavson 2021").

73 Liew 2016, *supra* note 25, at 956.

74 Ystrom 2017, *supra* note 72, at 6 (Table 2).

the epidemiologist[] who's in this case" (i.e., Dr. Baccarelli). (Louie Dep. 150:24-151:21.)

5. Dr. Hollander

Plaintiffs' expert in psychiatry, Dr. Hollander, espouses a novel "transdiagnostic" approach to causation. According to Dr. Hollander, because "[t]here is a strong interrelationship between the neurodevelopmental disorders of ASD and ADHD and across neurodevelopmental disorders," "it is appropriate to review" evidence measuring the symptoms of all such conditions. (Am. Rep. of Eric Hollander ("Hollander Am. Rep.") at 4, June 22, 2023 (Ex. 11).) In addition to vaguely referencing a "constellation of symptoms [he] see[s] in [his] patients" (*id.* at 11), Dr. Hollander primarily cites to an editorial, which he describes as "recent transdiagnostic research that shows shared neural, genetic, physiological, structural, and psychological traits" for various disorders, including anxiety, depression and bipolar disorder. (*Id.* at 11, 17.)

In his rebuttal report, Dr. Hollander attempts to perform a Bradford Hill analysis in which he simultaneously assesses whether acetaminophen causes ASD and ADHD, repeatedly conflating the two distinct conditions. (*See generally* Rebuttal Rep. of Eric Hollander ("Hollander Rebuttal Rep."), July 28, 2023 (Ex. 12).) Although Dr. Hollander claims that he undertook his own, independent analysis of general causation and the Bradford Hill factors (*see* Dep. of Eric Hollander ("Hollander Dep.") 162:17-21, 163:2-8, Aug. 9, 2023 (Ex. 13)), he expressly relied on Dr. Baccarelli for his causation opinion (*see id.* 161:15-162:4, 162:9-13) and was forced to refer to a table Dr. Baccarelli created more than a dozen times at his deposition when asked basic questions about the relevant studies (e.g., Brandlistuen 2013) (*see id.* 204:23-205:1 ("Let the record reflect that Dr. Hollander is going to Dr. Baccarelli's tables to answer my question."); *see also id.* 287:4-21 (similar)). When analyzing strength and consistency, Dr. Hollander never mentions the studies finding no association or those that would cast doubt on his opinions. (Saunders 2019, Leppert 2019, Hornig 2018.) Nor does he mention that Avella-Garcia

2016 found no statistically significant association between acetaminophen and ASD symptoms despite citing the same study for his ADHD opinions. (*See* Hollander Rebuttal Rep. at 13.)

Dr. Hollander's deposition testimony also demonstrates that he lacks basic familiarity with the opinions ***in his own report***. For example, although Dr. Hollander claims in his report that he relied on a "study showing the disparity in ASD rates in the United States compared to Cuba" that "tends to show that decreased APAP use in a population corresponds to a lower rate of ASD" (Hollander Rebuttal Rep. at 19), Dr. Hollander asserted at his deposition that he was not "relying on . . . diagnosis rates in Cuba . . . to support [his] opinions" (Hollander Dep. 137:5-16). Dr. Hollander also testified at his deposition that he disagreed with the assertion that "with respect to strength of association [criterion set forth by Bradford Hill], [he] view[s] the strength of a perceived association not by the magnitude but by the statistical significance" (Hollander Dep. 170:4-171:6), even though that sentence was read ***directly from his own report*** and describes his own stated approach to evaluating the strength of association criterion (*see* Hollander Rebuttal Rep. at 8 ("I view the strength of a perceived association not by magnitude, but by statistical significance, in determining causality.")).

ARGUMENT

Under Fed. R. Evid. 702, plaintiffs have the burden of showing that their experts' opinions are reliable (and satisfy the other requirements of admissibility) by a preponderance of the evidence. *See* Prop. Fed. R. Evid. 702.[75]

Rule 702 imposes a "gatekeeping" function on courts, which are tasked with "'ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand.'"

[75] Although the amendments to Rule 702 do not take effect until December, the preponderance standard "echoes the existing law" and is thus applicable to these motions. *Sardis*, 10 F.4th at 284.

In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig., 982 F.3d 113, 122-23 (2d Cir. 2020) ("*Mirena I*") (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 597 (1993)). "[T]he importance of [this] gatekeeping function cannot be overstated," *Sardis*, 10 F.4th at 283, because "[e]xpert evidence can be both powerful and quite misleading" to jurors. *Daubert*, 509 U.S. at 595 (citation omitted). Accordingly, it is an "abdication of [the] gatekeeping role" to sidestep close review of an expert's opinions based on tenuous assertions that these are "questions of weight and not admissibility." *Sardis*, 10 F.4th at 284 (quoting advisory committee's note to draft amendment to Rule 702).

In performing its gatekeeping function, a court must "take a hard look at plaintiffs' experts reports," which involves "a *rigorous examination* of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and methods to the case at hand." *Mirena I*, 982 F.3d at 123 (quoting *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002)). A court's review is not "limited to determining whether the expert relied upon a 'wide array' of evidence," but extends to a careful examination of "every aspect of the expert's analysis—including his methodology, the combination of facts and scientific evidence on which he relies, and the links between the evidence and his conclusions." *In re Zantac (Ranitidine) Prods. Liab. Litig.*, No. 20-2924, --- F. Supp. 3d ----, 2022 WL 17480906, at *65 (S.D. Fla. Dec. 6, 2022) (quoting *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1311-12 (N.D. Fla. 2018)), *appeal dismissed*, No. 23-10090, 2023 WL 2849068 (11th Cir. Mar. 22, 2023).

As set forth below, plaintiffs have failed to show that their experts' ASD opinions are reliable—and have certainly not done so by a preponderance of the evidence.

I. DRS. BACCARELLI, CABRERA, HOLLANDER AND LOUIE DO NOT RELIABLY IDENTIFY A "CLEAR-CUT" ASSOCIATION BETWEEN PRENATAL ACETAMINOPHEN EXPOSURE AND ASD.

"The first step in the causation analysis" is identifying "an association between two variables." *Mirena II*, 341 F. Supp. 3d at 265 (citation omitted). "In general, before concluding that there is a 'true' association between a medication and an adverse outcome, the teratology community requires repeated, consistent, statistically significant human epidemiological findings, and studies which address suspected confounders and biases." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 454 (E.D. Pa. 2014); *see also Wade-Greaux v. Whitehall Lab'ys, Inc.*, 874 F. Supp. 1441, 1453 (D.V.I. 1994) ("Absent consistent, repeated human epidemiological studies showing a statistically significant increased risk of particular birth defects associated with exposure to a specific agent, the community of teratologists does not conclude that the agent is a human teratogen."), *aff'd*, 46 F.3d 1120 (3d Cir. 1994). Plaintiffs' experts' causation opinions fail at this first step.

A. Drs. Baccarelli, Cabrera, Hollander And Louie Cherry-Pick, Misread And Twist Study Results.

"An expert must not cherry-pick from the 'scientific landscape and present the Court with what he believes the final picture looks like.'" *Daniels-Feasel*, 2021 WL 4037820, at *5 (citation omitted); *see also In re Zantac*, 2022 WL 17480906, at *57 ("[C]herry-picking of data demonstrates unreliability."). Rather, an expert is required to carefully "evaluate 'all of the scientific evidence.'" *Daniels-Feasel*, 2021 WL 4037820, at *5 (citation omitted). This includes not only accounting for studies that undercut the expert's conclusions, but also considering the "limitations" of the studies on which he relies. *Mirena II*, 341 F. Supp. 3d at 240-41 (citation omitted). Plaintiffs' experts violate these fundamental scientific principles.

1. Drs. Baccarelli, Cabrera, Hollander And Louie Do Not Account For Significant Limitations Of Their Cited Studies.

Plaintiffs' experts rely on two very limited studies in concluding that an association exists between prenatal acetaminophen exposure and a diagnosis of ASD. That does not suffice to satisfy the reliability requirement of *Daubert*.

Ji 2020. As explained above, Ji 2020 measured acetaminophen in maternal and umbilical cord blood samples at the time of birth; as the authors expressly cautioned, that measurement "may at most reflect maternal use of acetaminophen during the peripartum period."[76] (*See* Hollander Dep. 367:19-368:22 (biomarkers reflect blood supply "at the time of birth").) This is a critical flaw in their opinions because the lynchpin of plaintiffs' experts' approach to dose is Dr. Louie's speculative claim that "prenatal exposure to acetaminophen . . . for at least 28 cumulative days during pregnancy increases the risk of ASD/ADHD" (Louie Am. Rep. ¶ 28)—a period that Dr. Louie does not, and cannot, claim is reflected by the Ji 2020 results. Moreover, Dr. Cabrera testified that the most important time for neurodevelopment in humans is the second trimester (i.e., long before the mothers examined in Ji 2020 were found to have acetaminophen metabolites in their cord blood). (*See* Cabrera Dep. 23:13-24:2 (identifying the second trimester of pregnancy as the most sensitive time or "critical window of exposure"); *see also* Hollander Dep. 352:5-7 (second and third trimesters most important for ASD causation).)[77] In short, although the authors of Ji 2020 cautioned against misreading their results as reporting an association between exposure to acetaminophen through the gestational period and a diagnosis of ASD, that is exactly what plaintiffs' experts have done here.

Another challenge with interpreting Ji 2020 is that all the umbilical cord samples in the

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[76] Ji 2020, *supra* note 32, at 188.

[77] Dr. Baccarelli vaguely testified that the entire window of pregnancy is critical (Baccarelli Dep. 91:18-92:12, 92:23-93:24), putting him at odds with his fellow experts and highlighting that plaintiffs have no coherent theory of general causation in this litigation.

study contained acetaminophen, "which contradicts the common knowledge that only about half of pregnant women take acetaminophen, and certainly much less during the peripartum period." (Baccarelli Am. Rep. at 102.) One possible explanation for this facially bizarre finding is laboratory error. (*See* Rep. of Jennifer Pinto-Martin ("Pinto-Martin Rep.") at 45 (Ex. 14).) Another is that there were exposures "to acetaminophen through other sources such as drinking water." (*See* Baccarelli Am. Rep. at 102.) Such an explanation would comport with Dr. Cabrera's observations that the entire population is exposed to APAP through environmental sources. (*See* Cabrera Am. Rep. at 20.) As Dr. Cabrera recognizes, "because APAP is a metabolite of aniline, the wide-spread use of industrial aniline in the environment results in ***nearly universal human exposure to APAP***, although at very low levels" (*id.* (emphasis added)), raising substantial questions about the source of some of the acetaminophen found in the umbilical cord samples. *See In re Zantac*, 2022 WL 17480906, at *69 (excluding opinions of experts who agreed that "people can be exposed to NDMA from sources such as diet, water, and air" but relied on studies without explaining how the authors accounted for those sources).

Finally, with the exception of Dr. Cabrera, none of plaintiffs' experts addresses the authors' warning that they were "unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors."[78] *See, e.g.*, *Daniels-Feasel*, 2021 WL 4037820, at *8 (study's result cannot form the basis of a reliable causation opinion where the expert "fail[s] to mention" or unjustifiably "dismiss[es]" express admonitions by the author that confounding or bias might explain the result); *Mirena II*, 341 F. Supp. 3d at 262 (expert's failure to grapple with evidence concerning confounding factors rendered her causation opinion unreliable). That admonition is a serious concern in light of the significant, recognized role

[78] Ji 2020, *supra* note 32, at 188.

genetics play in the etiology of ASD. *See Hendrix*, 609 F.3d at 1202 ("The medical literature indicates that there are a dizzying array of other factors that have been mentioned as possible causes, including as many as 90 gene mutations that could play a role in the development of autism."); *see also Melnick*, 959 N.Y.S.2d at 620 ("peer-reviewed studies conducted with appropriate controls . . . bolster the generally accepted medical finding that autism/PDD is primarily a genetic or environmental disorder").[79] In fact, after adjusting for maternal mental health, the authors of Ji 2020 reported a remarkable decrease in association across each aOR such that neither the second tertile (aOR = 1.76, 95% CI 0.69-4.72, p-value = 0.25) nor the third tertile (aOR = 2.48, 95% CI 1.00-6.57, p-value = 0.06) of total acetaminophen burden was significantly associated with ASD diagnoses in children.[80]

Underscoring the importance of controlling for genetics in this context, sibling control studies have debunked prior theories that various exposures and events, including prenatal antidepressant exposure, labor-inducing medication and c-sections, were linked to ASD.[81] Although the majority of plaintiffs' experts have recognized the wisdom behind sibling controls (*see, e.g.*, Louie Dep. 114:19-115:13 (regarding sibling controls as a "better design"); Cabrera Dep. 268:8-19 (sibling control "is one manner of control" and "having controls is important" for high-quality studies)), Dr. Baccarelli asserts without any basis that the use of sibling-control analyses could lead to an under-estimation of a true association (Baccarelli Am. Rep. at 120). Dr. Baccarelli agrees it is "desirable" to control for confounders, but he asserts that the "sibling-

[79] Since *Hendrix*, researchers have uncovered hundreds of new common and rare genetic variants tied to ASD. *See* Rep. of Wendy Chung ("Chung Rep.") at 26-28, July 21, 2023 (Ex. 15).

[80] *See id.* at Supplementary eTable 3.

[81] *See, e.g.*, Vega, *Implementation of Advanced Methods for Reproductive Pharmacovigilance in Autism: A Meta-Analysis of the Effects of Prenatal Antidepressant Exposure*, 177(6) Am. J. Psychiatry 506 (2020); Oberg 2016, *supra* note 12; Curran 2015, *supra* note 12.

control design eliminates not only the impact of family factors that operate as confounders but also that of family factors that operate as mediators." (Baccarelli Am. Rep. at 118.) To Dr. Baccarelli, this means that sibling-control analyses necessarily "bias" the association toward the null. (*Id.*) However, for sibling-control designs to create such bias, exposures in the ***first*** pregnancy would have to influence the possible development of ASD in the second or subsequent pregnancies.[82] And Dr. Baccarelli has no evidence that taking acetaminophen in one pregnancy would somehow affect risks of ASD in subsequent pregnancies.[83]

In short, Drs. Baccarelli, Cabrera, Hollander and Louie do not meaningfully account for the Ji 2020 authors' "explicitly expressed limitations," effectively "press[ing] conclusions that the . . . authors were not willing to make, thereby demonstrating the unreliability of [their] own conclusions." *Daniels-Feasel*, 2021 WL 4037820, at *10.

Liew 2016. Drs. Baccarelli, Cabrera, Hollander and Louie also rely on Liew 2016, but there, the authors found no statistically significant association between prenatal acetaminophen exposure and ASD without HKD; they only found a statistically significant association for ASD with HKD. Infantile autism was likewise not significantly associated with acetaminophen exposure when taken as a whole or when broken down by cases without HKD and those with HKD. As the authors expressly cautioned, "[i]f ASD and hyperkinetic disorder are considered two different disorders with different etiologies, our results can be interpreted as acetaminophen only having an impact on hyperkinetic disorder but not ASD."[84] Indeed, this led Dr. Cabrera to

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82 *See* Sjölander, *Carryover Effects in Sibling Comparison Designs*, 27(6) Epidemiology 852 (2016).

83 The suggestion that taking a medication with a half-life of three hours in one pregnancy affects the risk of developing ASD in subsequent pregnancies serves to highlight the extreme nature of Dr. Baccarelli's opinions and the lengths to which he is willing to go to support his bottom-line conclusions. *See In re Zantac*, 2022 WL 17480906, at *127 ("Dr. McTiernan is alone in her methodology" in opining that "ranitidine epidemiology is unnecessary to answer the ranitidine question because dietary and occupational studies are sufficient.").

84 Liew 2016, *supra* note 25, at 954.

conclude that overall, the study found prenatal use of acetaminophen was associated with ASD accompanied by hyperkinetic symptoms "but not with other ASD cases." (Cabrera Am. Rep. at 131.) None of plaintiffs' other experts addresses this limitation in their report. Nor do they attempt to reconcile the weak reported association in Liew 2016 with the results of Ji 2020 (the centerpiece of their opinions), which reported no statistically significant increase in the risk of ASD with ADHD, but did report a statistically significant association between acetaminophen exposure and ASD without ADHD. These results are inconsistent because, as plaintiffs' own expert recognizes, "[b]oth ADHD and HKD refer to a combination of inattention, hyperactive, and impulsive behavior in children." (Hollander Am. Rep. at 41.) As a result, if there were a true association between in utero acetaminophen exposure and ASD with HKD, it would make no sense for the association to be absent for ASD and ADHD.[85]

Drs. Cabrera, Hollander and Louie also fail once again to meaningfully "acknowledg[e] the authors' explicitly expressed limitations." *Daniels-Feasel*, 2021 WL 4037820, at *10. Most notably, Liew 2016 cautioned that "residual confounding by indication or genetic factors [are] alternate explanations" for the small association reported between acetaminophen and ASD with HKD.[86] The only expert to address this limitation is Dr. Baccarelli, who downplays the authors' "alternate explanations" as a "theoretical possibility" that was "limit[ed]" by the study design's "control for confounders." (Baccarelli Am. Rep. at 99.) This justification is illogical because the study did not control for genetics, and it contravenes *Daubert*'s command that an expert may not simply "dismiss[]" express warnings by a study's author that confounding factors might explain the reported result. *Daniels-Feasel*, 2021 WL 4037820, at *8.

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[85] *See* Hollander Am. Rep. at 41 ("ADHD may also be referred to as Hyperkinetic Disorder (HKD) in some countries, and the terms may be used interchangeably.").

[86] Liew 2016, *supra* note 25, at 956.

2. Dr. Baccarelli, Cabrera, Hollander And Louie Fail To Account For The Majority Of Scientific Evidence Reporting No Association.

Plaintiffs' experts also "disregard[]" studies that "failed to report a statistically significant association" between acetaminophen exposure and ASD, further highlighting the unreliability of their methods. *Daniels-Feasel*, 2021 WL 4037820, at *8-9; *see also Daniels-Feasel*, 2023 U.S. App. LEXIS 19448, at *7-8 (rejecting causation opinions where the expert "cherry-picked only favorable studies" and failed to "discuss precisely why" purported shortcomings "in the studies he ignored was a big enough flaw to render them irrelevant"); *In re Lipitor (Atorvastatin) Calcium Mktg., Sales Pracs. & Prods. Liab. Litig.*, 145 F. Supp. 3d 573, 594 (D.S.C. 2015) (excluding general causation opinions that were "based on cherry-picked studies and the avoidance of all contrary evidence"). As discussed above, of the five studies that have evaluated the association between in utero acetaminophen usage and diagnosed ASD, three studies (Ji 2018, Saunders 2019 and Hornig 2018) ***showed no statistically significant association***. Indeed, one of the studies produced a point estimate below 1.0, suggesting that if there were any effect, it would be protective.[87] Drs. Hollander and Louie do not even mention these studies in their reports, and Drs. Baccarelli and Cabrera brush them aside without scientific justification. (*See, e.g.*, Baccarelli Am. Rep. at 99-101; Cabrera Am. Rep. at 131-32.)

Ji 2018. Drs. Cabrera, Hollander and Louie ignore this study, which concluded that "the risks of ASD diagnosis . . . were not significantly associated with maternal plasma levels of acetaminophen metabolites across all models."[88] As previously discussed, this finding is inconsistent with the same authors' conclusion two years later that cord blood levels of

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[87] *See* Hornig 2018, *supra* note 36, at 763 ("Here we found only small risk reduction with use of acetaminophen" compared to a "small increase in risk among febrile women who did not take acetaminophen.").

[88] Ji 2018, *supra* note 17, at 7.

acetaminophen were associated with ASD. Dr. Cabrera's failure to address this study's ASD findings is especially glaring because he cites Ji 2018 in support of his opinion that in utero acetaminophen exposure causes ADHD. (Cabrera Am. Rep. at 139.) This is classic "cherry-pick[ing]." *Daniels-Feasel*, 2023 U.S. App. LEXIS 19448, at *7.

After defense expert Dr. Pinto-Martin called out Dr. Baccarelli's failure to address the finding of no statistically significant association from Ji 2018 in his opening report, Dr. Baccarelli responded by twisting the results of Ji 2018 in his rebuttal report, essentially going so far as to claim that the study supports his opinions. Although Dr. Baccarelli acknowledges that the odds ratio of 1.39 was not "statistically significant," he states that "the point estimate indicates . . . that in the Ji 2018 study, women who had higher acetaminophen levels had a 39% increased risk of having a child with ASD." (Rebuttal Rep. of Andrea Baccarelli at 12, July 28, 2023 (Ex. 16).) That is not a proper way to interpret an epidemiologic study. *See In re Zantac*, 2022 WL 17480906, at *81 ("[T]he study author cannot conclude with 95% confidence . . . whether ranitidine actually confers a *protective effect* on the user . . . or a *detrimental effect* on the user—the part of the confidence interval to the right of the line. This uncertainty means . . . that the study finding is not helpful to a causation inquiry."). Notably, Dr. Baccarelli does not articulate any reason for "understating the importance of statistical significance" and "downplaying the possibility that [the insignificant positive results] support *no* association." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 799 (3d Cir. 2017) (affirming exclusion of an expert who inappropriately "classified insignificant odds ratios above one as supporting a 'consistent' causality result, downplaying the possibility that they support *no* association"); *see also, e.g.*, *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig.*, 892 F.3d 624, 641-42 (4th Cir. 2018) (affirming the exclusion of general causation

opinion regarding the drug Lipitor because the plaintiffs "failed to demonstrate that Dr. Singh's reliance on non-statistically significant 'trends' is accepted in [the] field" or has "served as the basis for any epidemiologist's causation opinion in peer-reviewed literature") (citation omitted); *Burst v. Shell Oil Co.*, No. 14-109, 2015 WL 3755953, at *12 (E.D. La. June 16, 2015) ("Dr. Infante's reliance on studies exhibiting results that are not statistically significant does not reliably support his opinion."), *aff'd*, 650 F. App'x 170 (5th Cir. 2016); *In re Zantac*, 2022 WL 17480906, at *128 ("[T]he [c]ourt concludes that Dr. McTiernan's high level of reliance upon statistically insignificant results is an 'undue reliance' that is indicative of an unreliable methodology."). This methodological failure further requires exclusion of Dr. Baccarelli's causation opinions.

Saunders 2019. Plaintiffs' experts also largely disregard this retrospective case-control study, which "focused on the presence of [various] environmental exposures during pregnancy in mothers of children diagnosed with autism spectrum disorder."[89] The study reported no association with ASD, and the difference between the ASD group and the control group was so small that the authors did not even report an odds ratio or confidence interval. Moreover, the study reported that use of ***other*** medications ***did*** have a statistically significant effect on ASD risks, with an odds ratio of 2.29 and a confidence interval of 1.29-4.36. This was true of environmental exposures like smoking (OR=2.56, 95% CI 1.91-5.49) as well.

Dr. Baccarelli states that "the study quality [of Saunders 2019] is extremely low" given its "retrospective case-control design with minimal consideration of epidemiological methods, including no consideration of any confounders, retrospective design, selection of controls through means different from those of the cases, and lack of adjustment for matching variables."

[89] Saunders 2019, *supra* note 21, at 1.

(Baccarelli Am. Rep. at 100-01.) But failure to control for confounding and retrospective case-control design (e.g., concerns over recall bias) would tend to artificially ***elevate*** any reported association, not ***diminish*** it. As previously discussed, controlling for such confounding factors has reduced observed associations between environmental exposures and the development of ASD. Moreover, similar limitations apply to the Liew 2016 and Ji 2020 studies on which he relies in reaching his conclusions—both of which expressly acknowledged that they were "unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors."[90] The fact that confounding factors only matter to Dr. Baccarelli when they support his ultimate conclusions "casts significant doubt on the reliability of both his weighting of the studies he reviewed . . . as well as his subsequent analyses." *Daniels-Feasel*, 2021 WL 4037820, at *9 (excluding opinion where expert "fail[ed] to address the fact that lack of compliance validation is a concern that was also noted by studies he cites for the existence of a statistically significant association"); *see also In re Zantac*, 2022 WL 17480906, at *131 (expert opinions were inadmissible, where, inter alia, they "t[ook] inconsistent positions" by criticizing follow-up time in the ranitidine studies while simultaneously "bas[ing] their opinions on dietary epidemiology with follow-up times comparable to, or even less than, ranitidine epidemiology"). And Dr. Baccarelli ***embraced*** retrospective studies at his deposition, reasoning that all memory is retrospective. (*See* Baccarelli Dep. 462:20-463:4 (remarking that "every record is retrospect. If [I] asked you whether you took Tylenol today, like, it would be retrospective, correct?"); *see also id.* 463:5-464:9.)

Hornig 2018. None of plaintiffs' experts except Dr. Baccarelli even considers this study, which evaluated the potential protective effect of acetaminophen used to treat fever and

[90] Ji 2020, *supra* note 32, at 188; *see also* Liew 2016, *supra* note 25, at 956.

ultimately reported that during the second trimester, treatment with the medication reduced the risk of fever such that it was no longer statistically associated with an increased risk of ASD.[91] (By contrast, the same study suggested that ibuprofen did not reduce the risk of ASD.[92])

Dr. Baccarelli minimizes the study on the ground that it "was not designed to assess the link between acetaminophen and ASD." (Baccarelli Am. Rep. at 99.) But regardless of its purpose, the study shows that fever is independently associated with the risk of developing ASD, reinforcing that indication by use (fever) is a significant confounder in other studies, as recently recognized by the FDA.[93] And although it is not clear whether the result reported by Hornig and his colleagues can be extrapolated to afebrile women, the apparent protective effect of acetaminophen, coupled with the lack of any such effect for ibuprofen, directly undermines Dr. Baccarelli's theory that acetaminophen is positively associated with ASD. Indeed, the authors expressly reported that "[r]isk tended to be lower within each trimester in febrile women who took acetaminophen for fever than in febrile women who did not," suggesting a "risk reduction with use of acetaminophen."[94] Dr. Baccarelli's attempt to brush this unfavorable finding aside is particularly concerning given that multiple other studies have similarly showed that acetaminophen attenuated the association between fever and ASD symptoms.[95]

In sum, the scientific community has not made "repeated, consistent, statistically

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91 Hornig 2018, *supra* note 36, at 762.

92 *Id.*

93 FDA 2023 Review, at 17 (noting that "fever and headache/migraine" share "collinearity with APAP use during pregnancy").

94 *Id.* at 762, 763.

95 *See* Liew, *Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study*, 27(6) Epidemiology 912, 915 (2016) ("Taking acetaminophen in pregnancy appeared to benefit children whose mothers reported fever in pregnancy, possibly due to acetaminophen treatment countering the negative impact of fever on child IQ scores."); *see also* Zerbo, *Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Development Delays? Results from the CHARGE Study*, 43 J. Autism Dev. Disord. 25, 30 (2013) (OR for ASD attenuated when taking acetaminophen).

significant human epidemiological findings" of an association between prenatal use of acetaminophen and ASD. *In re Zoloft*, 26 F. Supp. 3d at 454. To the contrary, three of the five epidemiological studies that address the proposed association between maternal acetaminophen use and ASD diagnosis show either no statistically significant association or a negative one, and the other two are both internally inconsistent and in tension with each other. Plaintiffs' experts' failure to "fit[] [their] own opinion[s] into the larger field of [acetaminophen] epidemiology" requires exclusion of their causation opinions. *In re Zantac*, 2022 WL 17480906, at *129.

B. Drs. Baccarelli, Cabrera, Hollander And Louie's Reliance On Studies That Do Not Use Clinical ASD Diagnoses As Endpoints Is Also Unreliable.

Given the paucity of directly relevant epidemiologic literature, Drs. Baccarelli, Cabrera, Hollander and Louie focus most of their reports on proxy studies that use screening tools to test for symptoms associated with NDDs, a few meta-analyses that attempt to pool those studies, and literature addressing the proposed association between acetaminophen and other neurodevelopmental conditions. As explained below, these studies—and plaintiffs' experts' selective reliance on them—cannot plug the holes in the relevant epidemiology.

1. Proxy Studies That Do Not Involve Clinical Diagnoses Of ASD Do Not Provide A Reliable Basis For General Causation Opinions.

Drs. Baccarelli, Cabrera, Hollander and Louie rely heavily on so-called "proxy" studies that use various screening tools and questionnaires that measure, *inter alia*, behavior, cognition, temperament, psychomotor development, IQ and attention. (*See* Cabrera Am. Rep. at 149-63; *see also* Baccarelli Am. Rep. at 104-12; Hollander Rebuttal Rep. at 11-13; Louie Am. Rep. ¶¶ 69-73.) These studies are not a reliable basis for plaintiffs' experts' general causation opinions.

First, plaintiffs' experts have no scientific grounds for extrapolating from proxy studies because they lack the requisite "fit" with the ultimate conclusions reached by the experts. *See Amorgianos*, 303 F.3d at 270 (citing *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d

147, 185 (E.D.N.Y. 2001)). In *Hendrix*, the court rejected an expert's reliance on a study that compared the autism screening results of infants with cerebellar injury to those without cerebellar injury. 255 F.R.D. at 601. As the court explained, "the simple autism screening tests used in the study did not affirmatively diagnose autism disorders and further testing would be necessary before a diagnosis could be confirmed." *Id.* The FDA has similarly recognized that studies attempting to measure proposed associations between environmental exposures and the development of ASD should "[a]ssess[] outcomes using a clinical diagnosis."[96]

Plaintiffs' experts generally agree with this principle. (*See* Hollander Dep. 307:20-308:21 (screening tools are not a valid substitute for "clinician diagnoses"); Cabrera Dep. 186:6-16 (agreeing that screening results are merely "informative"); *see also* Louie Dep. 71:5-12 (clinical diagnoses are "stronger[] information").) Nonetheless, they rely on these tools, which imprecisely measure such disparate outcomes as "drawing scores," "gross motor development," "language delay in girls," "performance IQ" and "conduct problems"—as proxies for clinical ASD diagnoses. (*See* Cabrera Am. Rep. at 163-64; *see also* Baccarelli Am. Rep. at 157-58 (relying on studies involving "a broad spectrum of conditions and symptoms").) This is particularly troubling because some of these outcomes (e.g., child IQ or somatic complaints) are not even relevant to an ASD diagnosis and thus would not be used for ASD screening. (*See* Hollander Dep. 351:5-14 (IQ is not a symptom of ASD or ADHD); *see also* Baccarelli Am. Rep. at 108 (intelligence "does not directly bear on ADHD or ASD").)

Moreover, to the extent certain behaviors are relevant to an ASD evaluation (e.g., peer relationship problems, compulsive behavior, attention difficulties), they are not specific to ASD; rather, they are also associated with a host of other NDDs, such as oppositional-defiant disorder,

[96] App. L to FDA 2023 Review.

conduct disorder, and intellectual disability. (*See* Baccarelli Am. Rep. at 43; *see also* Hollander Am. Rep. at 17 (noting some shared behaviors between bipolar disorder and ASD as well as OCD and ASD); Hollander Dep. 347:21-348:15 (hyperactivity "can be a symptom in other conditions").) In addition, many of the cited studies touch on only one or two of the nine diagnostic criteria required for a DSM-5 diagnosis of ASD.[97] As a result, these tests not only lack specificity with regard to ASD, but they are also inherently over-inclusive.[98]

Avella-Garcia 2016, which looked at six different tools, including the Childhood Autism Screening Test ("CAST")[99]—is emblematic of the problem. Although Dr. Baccarelli states that CAST has 100% sensitivity and 97% specificity for ASD with a cut-off of 15 or more points (Baccarelli Am. Rep. at 98), the same paper Dr. Baccarelli cites in support of these sensitivity and specificity numbers reports that CAST only has a positive predictive value of 50%.[100] In other words, just half of children who score 15 or above meet the criteria for a clinical diagnosis of ASD. Shortly after the Avella-Garcia 2016 study was published, Zeyan Liew (author of Liew 2016) and another prominent scientist published a commentary criticizing its findings, in which they noted that "the outcomes we study are not very well defined" and that conclusions regarding proposed associations should be "based on clinically diagnosed outcomes (ADHD and ASD) and with longer follow-up."[101]

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97 *See, e.g.*, Skovlund, *Language Competence and Communication Skills in 3-Year-Old Children After Prenatal Exposure to Analgesic Opioids*, 26 Pharmacoepidemiol. & Drug Safety 625 (2017) (language ability).

98 Brewer, *Autism Screening in Early Childhood: Discriminating Autism From Other Developmental Concerns*, 11 Frontiers in Neurology 1 (2020) (ASD screeners tend to be overinclusive and have low predictive validity for future diagnoses); Hyman, *Identification, Evaluation, and Management of Children With Autism Spectrum Disorder*, 145(1) Pediatrics 1, 7 (2020) ("Results of a screening test are not diagnostic; they help the primary care provider identify children who are at risk for a diagnosis of ASD and require additional evaluation.").

99 *See* Avella-Garcia, *Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms*, 45(6) Int'l J. Epidemiol. 1987 (2016) ("Avella-Garcia 2016").

100 *See* Williams, *The CAST (Childhood Asperger Syndrome Test): Test Accuracy*, 9(1) Autism 45 (2005).

101 Olsen & Liew, *Commentary: Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function*

Second, even if the screening tests were informative of a possible association, Drs. Baccarelli, Cabrera, Hollander and Louie cite them "selective[ly] and fail to represent the studies' underlying conclusions accurately," *Daniels-Feasel*, 2021 WL 4037820, at *15, ignoring or downplaying findings within those papers that acetaminophen is ***not*** associated with other potential ASD symptoms. For example, Dr. Cabrera touts the finding in Avella-Garcia 2016 that "taking acetaminophen during pregnancy may lead to more symptoms of Autism . . . in male children." (Cabrera Am. Rep. at 129.) But in so doing, Dr. Cabrera ignores that girls showed significantly lower CAST scores (i.e., fewer symptoms) and that the scores for all children were not significantly associated with in utero acetaminophen exposure.[102] Drs. Baccarelli and Hollander likewise fail to address these findings, which is particularly troubling given their reliance on Avella-Garcia 2016 as supposed support for their opinions on ADHD. (*See* Baccarelli Am. Rep. at 83 (stating that study was "well designed, conducted a comprehensive assessment of confounders . . . and had rich data"); *see also* Hollander Am. Rep. at 18.)[103]

Leppert 2019 (which used data from the same cohort as Avella-Garcia 2016)[104] is similarly ignored by Drs. Hollander and Louie and downplayed by Drs. Baccarelli and Cabrera. Leppert evaluated whether mothers who have higher polygenic risk scores ("PRS")[105] for ASD and ADHD are more likely to take acetaminophen during pregnancy. As part of their research,

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and Autism Spectrum Symptoms, 45(6) Int'l J. Epidemiol. 1996, 1997 (2016) ("Olsen & Liew Commentary").

[102] *See* Avella-Garcia 2016, *supra* note 99, at 1991.

[103] Olsen & Liew Commentary, *supra* note 101, at 1996. To the extent Avella-Garcia 2016 reported an association for males, the authors failed to account for "possible genetic confounding," which was a "main concern in Avella-Garcia's study." *Id.*

[104] *See* Leppert, *Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures*, 76(8) JAMA Psychiatry 834 (2019) ("Leppert 2019").

[105] Polygenic risk scores refer to "the integration of many common variants in many genes into a single score to predict disease risk." (Chung Rep. at 3.)

however, the Leppert authors also obtained data on in utero acetaminophen exposure and ASD symptoms and ultimately found ***no*** association between the two (RR=0.76, 95% CI 0.51-1.13).[106] Dr. Baccarelli states that this finding has no bearing on his opinions because the paper "aimed to investigate whether maternal genetic factors (polygenetic risk scores) for NDDs were associated with early-life exposures that have been previously linked to these disorders" rather than study "the association of prenatal acetaminophen and ASD." (Baccarelli Am. Rep. at 100.) But regardless of purpose, the finding still stands, and Dr. Baccarelli's failure to seriously account for it renders his opinion unreliable. Dr. Baccarelli also contends that the finding of no association "was only adjusted by child's age at the time of ASD assessment and sex," which was "not adequate to control [for] confounding." (Baccarelli Am. Rep. at 100.) As already discussed, however, failure to control for confounding would tend to artificially ***elevate*** any reported association and, in any event, similar limitations apply to the epidemiological studies on which Dr. Baccarelli relies. This highlights once again Dr. Baccarelli's "propensity to cherry-pick the findings he agrees with and his failure to acknowledge the express limitations that render those findings unreliable, while disregarding those studies that do not support his conclusions because they suffer from the same limitations." *Daniels-Feasel*, 2021 WL 4037820, at *9.[107]

Plaintiffs' experts also disregard key findings within the studies they cite. Although Dr. Baccarelli identifies 15 studies that allegedly bear on "neurodevelopmental" outcomes, including ASD (*see* Baccarelli Am. Rep. at 105-12), a number of those studies produced results that cannot be reconciled with the experts' conclusions. One such study is Tovo-Rodrigues 2020, which

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[106] Leppert 2019, *supra* note 104, at Supplementary eTable 8.

[107] Dr. Baccarelli's proffered justification for discounting the finding of no association in Leppert is illogical. As previously discussed, when other studies addressing the relationship between acetaminophen use and ASD (including Ji) adjusted for additional potential confounders, the observed association became weaker, not stronger.

examined neurodevelopment as measured by Battelle's Developmental Inventory ("BDI") and Child Behavior Checklist ("CBCL") and found no association with maternal acetaminophen use. Dr. Hollander ignores Tovo-Rodrigues's conclusion that the authors could not "confirm the existence of an association between acetaminophen used during pregnancy and low neurodevelopmental performance,"[108] even though Dr. Hollander considers the CBCL to be "a good Level 1 screener of ASD." (Hollander Rebuttal Rep. at 24-25.) Nor does he reconcile the inconsistent findings from Parker 2020, which similarly employed the CBCL; there, acetaminophen "use during pregnancy was weakly associated with mother-reported behaviour problems and ***not*** associated with teacher-reported problems" as measured by the Child Behavior Checklist and Teacher Report Form.[109]

In short, of the 15 non-diagnostic studies cited by Dr. Baccarelli (*see* Baccarelli Am. Rep. at 105-12), ***more than half*** reported ***no*** significant impairments or had mixed results. As a result, even if these sorts of screening test studies were a reliable proxy for assessing an association with ASD, plaintiffs' experts' "failure to reconcile data that does not support [their] conclusions" from the cited studies "casts doubt on the reliability of [their] opinion[s]." *Daniels-Feasel*, 2021 WL 4037820, at *15.

2. Drs. Baccarelli, Cabrera, Hollander And Louie's Reliance On Two Meta-Analyses Is Also Unreliable.

Drs. Baccarelli, Cabrera, Hollander and Louie also rely on two meta-analyses (Masarwa 2018 and Alemany 2021) that pooled some of the studies previously discussed. (*See, e.g.*,

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[108] Tovo-Rodrigues, *Low Neurodevelopment Performance and Behavioural/Emotional Problems at 24 and 48 months in Brazilian Children Exposed to Acetaminophen During Foetal Development*, 34 Paediatr. Perinat. Epidemiol. 278, 278 (2020).

[109] Parker, *Maternal Acetaminophen Use During Pregnancy and Childhood Behavioural Problems: Discrepancies Between Mother- and Teacher-Reported Outcomes*, 34(3) Paediatr. Perinat. Epidemiol. 299, 299 (2020) (emphasis added).

Baccarelli Am. Rep. at 103-04; Cabrera Am. Rep. at 163-68; Louie Am. Rep. ¶ 95; Hollander Rebuttal Rep. at 15.) Masarwa 2018 pooled five studies, only one of which (Liew 2016) actually measured clinically-diagnosed ASD, and derived a weak pooled risk ratio of 1.19 (95% CI 1.14-1.25).[110] And Alemany 2021 pooled data from six birth cohorts across Europe and reported a statistically significant association between acetaminophen and "ASD symptoms" of 1.19 (95% CI 1.07-1.33). [111] The findings of Liew (which contained data drawn from both screening tools and hospital diagnoses) accounted for 47% of Alemany 2021's findings—which were reduced to a non-significant level when diagnostic data from Liew were used in place of Liew's screening data. (*See* Hollander Dep. 292:25-293:25.)

These meta-analyses are not informative, as explained by Ricci (2023), because there are "an insufficient number of comparable studies"[112]—i.e., only five epidemiological studies have actually assessed the proposed relationship between maternal use of acetaminophen and ASD diagnosis, with the remainder of studies focusing on the disparate and non-specific results of screening tools. Notably, plaintiffs' experts do not even address Ricci 2023's statement with regard to ASD, even though they rely on that paper in opining that acetaminophen causes ADHD. (*See* Baccarelli Am. Rep. at 96.)

In any event, even if there were a sufficient number of homogeneous epidemiological studies on acetaminophen use and ASD to meta-analyze, a meta-analysis cannot eliminate or

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110 Masarwa, *Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies*, 187(8) Am. J. Epidemiol. 1817, 1825 (2018) ("Masarwa 2018").

111 *See* Alemany, *Prenatal and Postnatal Exposure to Acetaminophen in Relation to Autism Spectrum and Attention-Deficit and Hyperactivity Symptoms in Childhood: Meta-Analysis in Six European Population-Based Cohorts*, 36 Euro. J. Epidemiol. 993, 998 (2021) ("Alemany 2021").

112 Ricci 2023, *supra* note 70, at 482.

"fix" the limitations of the underlying studies. *See McLaughlin v. BNSF Ry. Co.*, 439 F. Supp. 3d 1173, 1184 (D. Neb. 2020). Indeed, "[c]onsidering the significant limitations inherent" in the underlying studies, the authors of Masarwa 2018 expressly warned against "overstating the significance of the results of [their] analysis."[113] Accordingly, these two meta-analyses do not provide reliable support for Drs. Baccarelli, Cabrera, Hollander and Louie's causation opinions.

3. Drs. Hollander, Baccarelli And Cabrera's "Transdiagnostic Approach" To NDDs Is Also Unreliable.

Plaintiffs' experts also invoke a so-called "transdiagnostic approach" to NDDs in an effort to compensate for the paucity of studies on the posited ASD association. Dr. Hollander, the key promoter of this theory, states that because "[t]here is a strong interrelationship between the neurodevelopmental disorders of ASD and ADHD and across neurodevelopmental disorders," "it is appropriate to review the body of evidence" that measures the symptoms of all such conditions. (Hollander Am. Rep. at 4.) Drs. Baccarelli, Cabrera and Louie echo him. (*See, e.g.*, Baccarelli Am. Rep. at 157-58; Cabrera Am. Rep. at 163-67.) Plaintiffs' experts' conflation of ADHD and ASD, which have distinct sets of diagnostic criteria, cannot be reconciled with Dr. Hollander's own acknowledgment that there are significant differences between "core symptoms" of the two conditions. (*See* Hollander Am. Rep. at 15.) This, too, renders their opinions unreliable. *See, e.g.*, *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) (reliance on evidence that bromocriptine causes ischemic strokes as support for claim that it also causes hemorrhagic strokes "is a 'leap of faith' supported by little more than the fact that both conditions are commonly called strokes"); *Burst*, 2015 WL 3755953, at *7 ("[S]tudies that do not examine the precise disease at issue may not provide good grounds for an expert's

[113] Masarwa 2018, *supra* note 110, at 1825.

opinion.").

Dr. Hollander cites an editorial, which he describes as "recent transdiagnostic research that shows shared neural, genetic, physiological, structural, and psychological traits" for both ASD and ADHD. (*Id.*)[114] But an "editorial is, to say the least, inadequate as a basis for a scientific judgment about the general causation of" anything. *Kilpatrick v. Breg, Inc.*, No. 08-10052, 2009 U.S. Dist. LEXIS 76128, at *22 (S.D. Fla. June 26, 2009), *aff'd*, 613 F.3d 1329 (11th Cir. 2010). In any event, the editorial he cites does not even discuss ASD or ADHD. Rather, as Dr. Hollander conceded at his deposition, the editorial addresses conditions like schizophrenia, bipolar disorder and major depression. (Hollander Dep. 343:22-344:2.) And even assuming that the editorial could be construed as "talking about a transdiagnostic approach to neuropsychiatric disorders" generally (as Dr. Hollander insists) (*id.* 344:13-15), the author warned that any such approach "will require a solid evidence base upon which to build,"[115] an evidentiary predicate Dr. Hollander has not satisfied with regard to ASD and ADHD.

Dr. Hollander also points to a 2023 research paper that purportedly identified similar brain biology among children with ASD, ADHD or OCD. (Hollander Am. Rep. at 12.)[116] But that article does not offer any claims about what environmental factors may be associated with either condition, much less cause each one,[117] meaning that Dr. Hollander is "press[ing] conclusions that the [study's] authors were not willing to make." *Daniels-Feasel*, 2021 WL 4037820, at *10. Moreover, the article specifically notes that the "overlap in neurobiology exists

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114 Citing Barch, *What Does It Mean to Be Transdiagnostic and How Would We Know?*, 177(5) Am. J. Psychiatry 370 (2020).

115 *Id.* at 372.

116 Citing Vandewouw, *Identifying Replicable Subgroups in Neurodevelopmental Conditions Using Resting-State Functional Magnetic Resonance Imaging Data*, 6(3) JAMA Network Open 1 (2023).

117 *See generally id.*

not only across conditions [i.e., ASD and ADHD], but also across typical development,"[118] suggesting that even those not diagnosed with ADHD or ASD share similar brain biology associated with the two conditions. If anything, this finding only highlights the imprecise and over-inclusive nature of plaintiffs' experts' approach to NDDs, each of which requires unique clinical diagnoses rather than short-cuts like those being espoused by plaintiffs' experts.

In short, Drs. Hollander, Baccarelli and Cabrera's reliance on a transdiagnostic approach "is a 'leap of faith' supported by little more than the fact that" ADHD and ASD are both NDDs. *Rider*, 295 F.3d at 1202. That does not suffice to satisfy *Daubert*.

II. DRS. BACCARELLI, CABRERA AND HOLLANDER DID NOT CONDUCT RELIABLE BRADFORD HILL ANALYSES.

The nine Bradford Hill considerations "form the generally accepted set of criteria by which, when reliably applied, modern practicing epidemiologists assign causality to an association." *Daniels-Feasel*, 2023 U.S. App. LEXIS 19448, at *5 (citation omitted); *see also Mirena II*, 341 F. Supp. 3d at 242 ("The Bradford Hill criteria are metrics that epidemiologists use to distinguish a causal connection from a mere association.") (quoting *In re Zoloft*, 858 F.3d at 795).[119] Importantly, these criteria only come into play when scientists have identified a "perfectly clear-cut" association in the epidemiologic literature. *Mirena II*, 341 F. Supp. 3d at

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[118] *Id.* at 11.

[119] Drs. Pearson and Louie do not offer a Bradford Hill analysis or any other comprehensive synthesis of the epidemiology on acetaminophen and ASD (or ADHD). Instead, it is apparent that their roles are more limited—in Dr. Pearson's case, to address potential biological mechanisms, and in Dr. Louie's, to address the level of exposure that purportedly can cause injury. These opinions are not admissible for the reasons set forth in defendants' Biological Plausibility and ADHD *Daubert* briefs and in other sections of this brief. But to the extent Drs. Pearson or Louie intend to offer a broader, stand-alone general causation opinion (whether as to ASD or ADHD), such opinions are separately inadmissible because they have not employed any recognized methodology (whether the Bradford Hill framework or some other reliable methodology) for doing so. *See In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1233 n.5 (D. Colo. 1998) (excluding causation opinion where "experts have not addressed the Bradford-Hill criteria at all" for "establish[ing] scientific cause and effect").

265.[120] As set forth in Section I, above, the data here do not show anything close to a "perfectly clear-cut" association.

Drs. Baccarelli, Cabrera and Hollander nonetheless each purport to apply the nine Bradford Hill considerations (*see, e.g.*, Baccarelli Am. Rep. at 158-72; Cabrera Am. Rep. at 189-95; Hollander Rebuttal Rep. at 14-21) to support their causality opinions. These analyses are unreliable and should be excluded from trial. *Daniels-Feasel*, 2023 U.S. App. LEXIS 19448, at *6 ("the district court should undertake a *rigorous examination* of" the expert's application of the Bradford Hill criteria).

As an initial matter, the experts' analyses improperly conflate ASD, ADHD and NDDs generally. (Baccarelli Am. Rep. at 173; *see also id.* at 158-72 (conducting Bradford Hill analysis as to "In Utero Acetaminophen Exposure and Neurodevelopmental Disorders"); Cabrera Am. Rep. at 189-95 (similar and addressing the causal relationship between acetaminophen "and neurodevelopmental toxicity"); Hollander Am. Rep. at 14-21 (similar).) In so doing, the experts "leav[e] obscure" how much weight they gave to the evidence on ***ADHD*** in formulating their conclusions as to ***ASD***, much less how such evidence factored into their treatment of the individual Bradford Hill factors. *Mirena II*, 341 F. Supp. 3d at 248; *see also In re Zantac*, 2022 WL 17480906, at *126 (excluding "vague and malleable" Bradford Hill analysis). This "effectively disables a finder of fact from critically evaluating [their] work," *Mirena II*, 341 F. Supp. 3d at 248, rendering each expert's proffered Bradford Hill analysis inherently unreliable.

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[120] *See also, e.g.*, *Hoefling v. U.S. Smokeless Tobacco Co.*, 576 F. Supp. 3d 262, 273 n.4 (E.D. Pa. 2021) (it would not "have been appropriate to apply [the Bradford Hill factors] here: scientists are to do so only after an epidemiological association is demonstrated"); *Frischhertz v. SmithKline Beecham Corp.*, No. 10-2125, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012) ("Dr. Goldstein attempted to use the Bradford-Hill criteria to prove causation without first identifying a valid statistically significant association. . . . Hence, Dr. Goldstein's general causation opinion is not reliable."); *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) ("Sir Bradford Hill identified the starting point of his criteria as 'an association between two variables' that is 'perfectly clear-cut and beyond what we would care to attribute to the play of chance.'") (citation omitted).

As detailed below, Drs. Baccarelli, Cabrera and Hollander's Bradford Hill analyses should also be excluded because they approach each of the individual Bradford Hill factors in an unscientific, results-oriented manner.

A. The Conclusion By Drs. Baccarelli, Cabrera And Hollander That A Facially Weak Association Supports The Strength Requirement Is Patently Unreliable.

"The strength of association factor is a 'gating' factor that 'requires a statistical, or strong, association between the cause under review and its asserted effect.'" *Daniels-Feasel*, 2021 WL 4037820, at *8 (quoting *Mirena II*, 341 F. Supp. 3d at 258 ("This factor is a necessary, or gating, factor for any Bradford Hill analysis to proceed, such that, if such a statistical association is not found, there is no charter to undertake a Bradford Hill analysis at all.")). To the extent studies have reported ***any*** increase in the risk of childhood ASD or even ASD-related symptoms among children whose mothers used acetaminophen during pregnancy, one found a moderate association (Ji 2020); the remainder found very weak associations: Liew 2016 reported a crude hazard ratio of 1.22 and an adjusted hazard ratio of 1.19,[121] and both meta-analyses of ASD symptoms reported risk or odds ratios of 1.19.[122] These relative risks are a far cry from the examples of a nine, ten, or even ***200***-fold increase in risk that Hill originally identified as supportive of causation,[123] and are "undeniably . . . not a strong association." *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prods. Liab. Litig.*, 424 F. Supp. 3d 781, 796 (N.D. Cal. 2020) ("the risk factor that emerged across all the studies was somewhere around 1.2," which

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121 *See* Liew 2016, *supra* note 25, at 955.

122 *See, e.g.*, Masarwa 2018, *supra* note 110, at 1820; Alemany 2021, *supra* note 111, at 998. Ji 2020 reported higher odds ratios, but that study is an outlier for all of the reasons previously discussed.

123 *See* Hill, *The Environment and Disease: Association or Causation?* 295, 297 (1965) ("Hill 1965").

"undeniably is not a strong association").[124]

Plaintiffs' own expert, Dr. Cabrera, characterizes the reported associations as being, at most, "moderate" and primarily "low." (Cabrera Am. Rep. at 134, 189 (acknowledging that "an odds ratio between 1 and 2 is deemed low").) Drs. Cabrera, Baccarelli and Hollander nevertheless claim that the strength-of-association factor is somehow satisfied by combining the limited number of studies involving ASD with the far greater number of those addressing ADHD. (*See, e.g.*, Cabrera Am. Rep. at 189 (referencing "[n]umerous studies" involving ADHD); Baccarelli Am. Rep. at 173 ("Numerous studies have shown a strong, statistically significant association between prenatal acetaminophen exposure and ADHD or ASD."); Hollander Rebuttal Rep. at 15 (similar).) As discussed above, relying on literature purportedly establishing an association between acetaminophen and ADHD as a basis for showing a similar relationship between the medication and ASD is unscientific, and such approaches have led other courts to exclude expert testimony. *See, e.g.*, *Rider*, 295 F.3d at 1202 (reliance on evidence that bromocriptine causes ischemic strokes as support for claim that it also causes hemorrhagic strokes "is a 'leap of faith'"); *Burst*, 2015 WL 3755953, at *7 ("[S]tudies that do not examine the precise disease at issue may not provide good grounds for an expert's opinion.").

Dr. Baccarelli also attempts to elide the undeniably weak risk ratios on the ground that "[e]xposures that are common can cause high numbers of cases even with small relative risks," offering the example of secondhand smoke and cancer. (Baccarelli Am. Rep. at 24.) But the fact

[124] *See also, e.g.*, *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1320-21 (9th Cir. 1995) ("For an epidemiological study to show causation under a preponderance standard, 'the relative risk of limb reduction defects arising from the epidemiological data . . . will, at a minimum, have to exceed "2."'") (citation omitted); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1356 (N.D. Ga. 2001) ("Thus, in the world of epidemiology, the threshold for concluding that an agent was more likely than not the cause of a disease is a relative risk greater than 2.0."); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002) ("[T]he threshold for concluding that an agent was more likely than not the cause of an individual's disease is a relative risk greater than 2.0.") (citation omitted), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).

that some low elevations in risk have been regarded as causal where other Bradford Hill factors—such as dose-response, consistency and biological plausibility—were particularly compelling does not mean that all low observed associations should be considered causal. To the contrary, it is a fundamental principle of epidemiology (and a premise of the Bradford Hill framework) that "lower relative risks" must be "scrutinize[d] . . . more closely." *See, e.g.*, *RMSE*, at 602; *cf. Magistrini*, 180 F. Supp. 2d at 606 ("[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence . . . ."). This is so "because there is a greater chance that they are the result of uncontrolled confounding or biases." *LeBlanc v. Chevron USA, Inc.*, 513 F. Supp. 2d 641, 648 (E.D. La. 2007) ("Although lower relative risks can reflect causality, the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases."), *vacated and remanded on other non-relevant grounds*, 275 F. App'x 319 (5th Cir. 2008) (per curiam). And because none of plaintiffs' experts has conducted a systematic review of the literature with respect to secondhand smoke, they are in no position to say that the evidence supporting causal associations for those exposures is of similar quality to the data on acetaminophen use.

Dr. Baccarelli also contends that "the number of studies that have consistently found a statistically significant association weighs heavily in support of this factor." (Baccarelli Am. Rep. at 159.) As previously discussed, however, most of the studies using an ASD diagnosis as an endpoint have found ***no*** association at all. And in any event, this contention erroneously conflates strength of association with consistency, which are analytically distinct, reflecting a fundamental misapplication of the Bradford Hill framework. *See In re Viagra*, 424 F. Supp. 3d at 796 (excluding Bradford Hill analysis where expert based her finding of strength of association on "the fact that a positive association was shown in all the studies," which "would at most go to

the 'consistency' factor under Bradford Hill").

In sum, Drs. Baccarelli, Cabrera and Hollander improperly find that the strength-of-association consideration is satisfied. And because strength of association is a "gating" factor, this alone requires exclusion of their general causation opinions. *See, e.g.*, *In re Viagra*, 424 F. Supp. 3d at 796 ("assign[ing] significant weight to the 'strength of association' factor" when reported relative risk was approximately 1.2 was unreliable); *In re Zoloft*, 26 F. Supp. 3d at 463 (excluding general causation opinion where, inter alia, "the strength of the associations . . . [wa]s weak, often not greater than one would expect by chance alone").

B. Drs. Baccarelli, Cabrera And Hollander Use Unreliable Methodologies To Conclude That The Studies Are Consistent.

Consistency of association means that "[d]ifferent studies that examine the same exposure-disease generally should yield similar results,"[125] and that an association should be "repeatedly observed by different persons, in different places, circumstances and times."[126]

Contrary to the FDA, which recently reaffirmed that the literature on the proposed association between maternal acetaminophen use and the development of ASD "remain[s] mixed"[127]—i.e., inconsistent—Drs. Cabrera, Baccarelli and Hollander all opine that consistency of association is "certainly" satisfied. (Baccarelli Am. Rep. at 161; *see also* Cabrera Am. Rep. at 190-91; Hollander Rebuttal Rep. at 15-16.) In order to reach that conclusion, they blatantly distort the scientific evidence in a results-driven manner. As noted above, of the five studies that evaluated an ASD diagnosis as an endpoint, three found ***no*** association;[128] one study found a

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125 *RMSE*, at 604.

126 Hill 1965, *supra* note 123, at 296.

127 FDA 2023 Review, at 3.

128 *See, e.g.*, Ji 2018, *supra* note 17; Saunders 2019, *supra* note 21; Hornig 2018, *supra* note 36.

statistically significant weak association;[129] and one found a moderate association (contrary to the findings of the same authors in a study of the same cohort just two years earlier).[130] Moreover, even studies that have reported an increased risk are internally inconsistent. For example, Liew 2016 found an association with ASD generally and ASD with HKD, but not ASD without HKD. By contrast, Ji 2020 reported no significant association between acetaminophen and ASD comorbid with ADHD (a condition similar to ASD with HKD), although acetaminophen was associated with both ASD and ADHD independently.

The studies involving screening tools are equally inconsistent. As previously discussed, Leppert 2019 did not find a statistically significant association between in utero acetaminophen exposure and ASD symptoms, while Avella-Garcia 2016 reported an increased risk of such symptoms in male children, but not in females. In addition, the studies using the CBCL reported conflicting results with respect to the portion of the test that focuses on behavior problems: one study found no association across the board;[131] another reported an association across the board;[132] and a third concluded that there was an association with "internalizing" behavior problems, but not "externalizing" ones.[133]

Drs. Cabrera and Hollander do not address any of these inconsistent findings, while Dr. Baccarelli takes the position that the findings are consistent if statistical significance is ignored. (Baccarelli Am. Rep. at 27 ("[A] set of results is consistent even if some of the results are not

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129 Liew 2016, *supra* note 25.

130 Ji 2020, *supra* note 32.

131 Vlenterie, *Neurodevelopmental Problems at 18 Months Among Children Exposed to Paracetamol In Utero: A Propensity Score Matched Cohort Study*, 45(6) Int'l J. Epidemiol. 1998 (2016) ("Vlenterie 2016").

132 Brandlistuen 2013, *supra* note 71, at 1705.

133 Trønnes, *Prenatal Paracetamol Exposure and Neurodevelopmental Outcomes in Preschool-Aged Children*, 34(3) Paediatr. Perinat. Epidemiol. 247 (2020).

statistically significant.").) As previously discussed, however, statistical significance is "an important metric to distinguish between results supporting a true association and those resulting from mere chance." *In re Zoloft*, 858 F.3d at 793-94, 799 (affirming exclusion of expert who inappropriately "classified insignificant odds ratios above one as supporting a 'consistent' causality result, downplaying the possibility that they support *no* association"). Plaintiffs' experts' result-oriented dismissal of statistical significance reflects an unreliable methodology. *See In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, MDL No. 2342, 2015 WL 7776911, at *10 (E.D. Pa. Dec. 2, 2015) ("[S]elective emphasis on trends and general consistency only when such concepts support [expert's] opinion is one example of 'situational science' which renders [expert's] opinion unreliable.").[134]

In any event, even if there were a scientific basis for disregarding the long-established concept of statistical significance, the data would still not support Dr. Baccarelli's position because the results reported in the scientific literature are not even directionally consistent. For example, multiple studies (Hornig 2018 and Leppert 2019) produced point estimates below 1.0, suggesting that acetaminophen had a ***protective*** effect.[135] In short, plaintiffs' experts' position on this critical Bradford Hill criteria is essentially that "consistency" means its opposite, which further highlights the unreliability of their opinions.

C. Drs. Baccarelli, Cabrera And Hollander Downplay The Specificity Requirement Without Any Scientific Basis.

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[134] *See also, e.g.*, *In re Lipitor*, 892 F.3d at 642 (affirming exclusion of general causation opinion regarding the drug Lipitor because the plaintiffs "failed to demonstrate that Dr. Singh's reliance on non-statistically significant 'trends' is accepted in [the] field") (citation omitted)); *In re Zantac*, 2022 WL 17480906, at *128 ("[T]he [c]ourt concludes that Dr. McTiernan's high level of reliance upon statistically insignificant results is an 'undue reliance' that is indicative of an unreliable methodology.").

[135] Avella-Garcia 2016 similarly reported a β of -0.51 for acetaminophen use and CAST scores in females, suggesting a protective effect as well. *See* Avella-Garcia 2016, *supra* note 99, at 1991.

"Specificity, in laymen's terms generally means that an agent usually causes one type of human [disease]. When an agent is associated with a broad array of different types of diseases it weakens the evidence because it is non-specific." *Gannon v. United States*, 571 F. Supp. 2d 615, 626 (E.D. Pa. 2007), *aff'd*, 292 F. App'x 170 (3d Cir. 2008).

Drs. Baccarelli, Cabrera and Hollander expressly concede that "[t]he association between APAP exposure and ASD or ADHD is not specific since APAP exposure is common and can cause other toxicities, including hepatoxicity." (Cabrera Am. Rep. at 191; *accord* Baccarelli Am. Rep. at 162 ("[T]he specificity criterion is not satisfied here."); Hollander Rebuttal Rep. at 19 ("I do not find that the association meets the specificity element.").) Instead, they declare that "modern epidemiologists" have deemed specificity to be "all but irrelevant" in assessing causality. (Baccarelli Am. Rep. at 162; *see also* Hollander Rebuttal Rep. at 3-4 (calling it "widely considered weak or irrelevant").) In particular, Dr. Baccarelli relies on Hill's statement that scientists should not "over-emphasize the importance of" specificity. (Baccarelli Am. Rep. at 162 (quoting Hill 1965 at 297).) But that statement is a far cry from declaring specificity a dead letter. As courts have recognized, the degree of specificity remains highly relevant because "the vast majority of agents do not cause a wide variety of effects." *Davis v. McKesson Corp.*, No. 18-1157 et al., 2019 WL 3532179, at *34 (D. Ariz. Aug. 2, 2019) (citation omitted).

Dr. Baccarelli also relies on Hill's acknowledgment that "tobacco smoking does not exhibit 'specificity' with respect to lung cancer—since smoking causes more diseases than just lung cancer." (Baccarelli Am. Rep. at 162 (citing Hill 1965 at 297).) But there is a "good reason why inferences about the health consequences of tobacco do not require specificity: Because tobacco and cigarette smoke are not in fact single agents but consist of numerous harmful agents, smoking represents exposure to multiple agents, with multiple possible effects." *RMSE*, at 606.

Here, by contrast, plaintiffs' claims center on a single agent—acetaminophen—which Drs. Baccarelli, Cabrera and Hollander insist causes ASD, ADHD, other unspecified NDDs and even non-neurodevelopmental conditions.

D. Drs. Baccarelli, Cabrera And Hollander Are Unable To Reliably Identify A Dose Response.

In assessing the dose-response (or biological gradient) criterion, scientists evaluate whether "a dose-response relationship [has] been established, i.e., does the magnitude of the response increase as the magnitude of the dose increases?" *Amorgianos*, 137 F. Supp. 2d at 168. This consideration is essential because "[t]he toxicity of any substance depends critically on the dose to which a human being is exposed and for what duration." *Id.* 168, 188 (excluding general causation expert who cited literature in which "[f]ew, if any, dose-response relationships were reported"); *see also, e.g.*, *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (11th Cir. 2005) (dose response is considered by some to be the "single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect") (citation omitted). As explained below, Drs. Baccarelli, Cabrera and Hollander misrepresent the scientific literature on the fundamental question of dose response.

Drs. Baccarelli, Cabrera and Hollander assert that "virtually every study that was powered to evaluate, and did in fact evaluate, dose response found such an association between the number of days of prenatal acetaminophen use or its cumulative dose and NDDs in children." (Baccarelli Am. Rep. at 163; *see also* Cabrera Am. Rep. at 191 (meta-regression analyses show "[t]he biological gradient criterion is met for ASD"); Hollander Rebuttal Rep. at 13, 18 (claiming that evidence of "dose-response relationships in multiple high-quality studies provides clear evidence of causation").) As Dr. Baccarelli acknowledges, however, only "two studies assessed dose response for ASD" (Ji 2020 and Liew 2016). (Baccarelli Am. Rep. at 163.) Given the

paucity of ASD-related dose-response studies, plaintiffs' experts rely primarily on "six studies [that] assessed dose response for ***ADHD***" and three that examined dose response for "general neurodevelopment." (*Id.* (emphasis added); *see also* Cabrera Am. Rep. at 191 (relying on "meta-regression analyses" that primarily examined ADHD).) As already discussed, plaintiffs' experts' conflation of disparate disorders and the literature addressing them is the antithesis of a reliable opinion. And although they cite to a couple of ASD-diagnosis studies that did attempt to assess dose response, plaintiffs' experts "misrepresent[] the underlying epidemiological data that [the experts] claim[] supports [their] opinion[s]." *Daniels-Feasel*, 2021 WL 4037820, at *17. For example, Dr. Baccarelli states that Liew 2016 "assessed dose response for ASD" (Baccarelli Am. Rep. at 163); however, at 2-5 weeks use, the reported association was 1.23 (95% CI 1.02-1.49), which ***declined*** to 1.16 (95% CI 0.91-1.48) for 6-20 weeks of use. That is the precise opposite of a dose response.

Drs. Baccarelli, Cabrera and Hollander do not address findings of other studies that undercut their opinions on dose response. Most notably, the Avella-Garcia 2016 study reported that neither "sporadic" nor "persistent" use of acetaminophen was associated with a significant change in CAST scores.[136] Plaintiffs' experts' "failure to reconcile data that does not support [their] conclusions" with findings that they claim do support them further "casts doubt on the reliability of [their] opinion[s]." *Daniels-Feasel*, 2021 WL 4037820, at *15.

E. Drs. Baccarelli, Cabrera And Hollander Do Not Offer Reliable Opinions About Biological Plausibility.

Plaintiffs' experts' opinions regarding biological plausibility are unreliable and inadmissible for all the reasons set forth in defendants' Biological Plausibility Brief,

[136] Avella-Garcia 2016, *supra* note 99.

incorporated herein. As a threshold matter, scientists do not understand the anatomical or biomechanical mechanism that gives rise to the development of ASD. *See Mirena II*, 341 F. Supp. 3d at 285 (expert must explain "the threshold issue of what [the disease] is and how this condition comes about"); *Hendrix*, 255 F.R.D. at 602 ("[U]ntil such time as medical science understands the physiological process by which autism develops and how the process occurs, the law cannot impose liability for autism."). Because "the precise cause" of ASD "is unknown," *Daniels-Feasel*, 2021 WL 4037820, at *2, plaintiffs' experts cannot demonstrate that any of their proposed mechanisms is plausible, *see Hendrix*, 255 F.R.D. at 599, 602 (excluding opinions on proposed "mechanism by which brain injury causes autism" because "identifying a cause of autism does not appear to be within the realm of current medical science").

Plaintiffs' experts' opinions are also unreliable because they support each of their speculative hypotheses by cherry-picking favorable studies, while ignoring those that reach contrary results. For example, plaintiffs' first theory relates to oxidative stress, and a claimed reduction in the antioxidant glutathione ("GSH"). But plaintiffs' experts either ignore or misrepresent multiple studies showing that acetaminophen does not actually decrease GSH levels or increase oxidative stress in the brain, and instead rely on far less relevant literature. In addition, the experts fail to link the scattered, cherry-picked neurochemical findings they do report to ASD, the disorder that their proposed biological mechanism is supposed to cause. Rather, they simply assume (without any scientific support) that any identifiable change in brain chemistry must cause ASD.

Dr. Ann Bauer aptly described biological theories as to how acetaminophen use might cause ASD or ADHD as mere "hypotheses."[137] Because unproven hypotheses do not suffice to

[137] Bauer, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Review*, 101 Horm. Behav. 125

satisfy biological plausibility under *Daubert*, plaintiffs' experts' opinions are unreliable with respect to this consideration as well. *See Doe*, 440 F. Supp. 2d at 474 ("conditional statement" in literature about "one possible mechanism by which early mercury exposures could increase the risk of autism" amounted to "hypothesis and speculation," failing the requirements of Rule 702) (citations omitted); *see also In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007) ("[A] biological explanation without evidence of the mechanism by which it works is merely an unproven hypothesis, a theory.").

F. The Literature Is Incoherent.

Coherence means that "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease."[138] Dr. Cabrera opines that this factor is satisfied because "[a] causal relationship . . . is consistent with the expected timing and results of exposure"—i.e., "we would expect that exposure during key developmental windows would produce harm." (Cabrera Am. Rep. at 192.) But research has not established what those "key developmental windows" are. While Dr. Cabrera postulates that the second trimester is the most "critical" period (Cabrera Dep. 23:13-24:2), Dr. Baccarelli testified that there is no particular critical exposure window, going so far as to claim that acetaminophen can cause ASD from the time of conception up to the point just prior to birth. (*See* Baccarelli Dep. 91:18-92:12, 92:23-93:24.) The notion that acetaminophen has the same purportedly causative impact on ASD nine months into a pregnancy as it does on the day an egg is fertilized is nonsensical. And the fact that plaintiffs' own experts are unable to agree on such a critical, threshold issue lays bare that they have no coherent theory of general causation,

(2018).

138 Hill 1965, *supra* note 123, at 298.

let alone one that is consistent with the body of epidemiological literature.

Dr. Baccarelli also states that "a causal association is coherent with the sudden and significant rise in the rates of NDDs seen over the past several decades." (Baccarelli Am. Rep. at 165.) However, Dr. Baccarelli disregards far more likely explanations for such a rise, including expansion of the diagnostic criteria for ASD and increased efforts to diagnose children early in life.[139] Studies have demonstrated that the broadening of diagnostic criteria and inclusion of the subthreshold diagnosis Pervasive Developmental Disorder—Not Otherwise Specified ("PDD-NOS") have been a driving force behind the increasing prevalence of clinically diagnosed ASD.[140] Studies have also found that advances in diagnostic capabilities, greater recognition of ASD and early and improved intervention have played an important role in ASD prevalence.[141] And changes in special education laws (including adding ASD as a serviceable diagnosis under the Individuals with Disabilities Education Act) have incentivized families and clinicians to obtain ASD diagnoses to facilitate access to educational services.[142] For these reasons, too, Dr. Baccarelli's approach to coherence is overly simplistic and unreliable.

G. Drs. Baccarelli, Cabrera And Hollander's Opinions On Temporality Are Speculative.

Plaintiffs' experts also cannot opine with any valid scientific basis that temporality is satisfied. As discussed in connection with coherence, Drs. Baccarelli, Cabrera and Hollander

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139 American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), 1994.

140 Tidmarsh & Volkmar, *Diagnosis and Epidemiology of Autism Spectrum Disorders*, 48(8) Can. J. Psychiatry 517 (2003).

141 Sheldrick, *Effectiveness of Screening in Early Intervention Settings to Improve Diagnosis of Autism and Reduce Health Disparities*, 176(3) JAMA Pediatrics 262 (2022); Wazana, *The Autism Epidemic: Fact or Artifact?*, 46(6) J. Am. Acad. Child Adolesc. Psychiatry 721 (2007).

142 Croen, *Descriptive Epidemiology of Autism in a California Population: Who is at Risk?*, 32(3) J. Autism Dev. Disord. 217 (2002).

fundamentally disagree on when the most vulnerable period for fetal development occurs, making it virtually impossible to know whether maternal exposure to acetaminophen in various studies actually preceded the biological changes that lead to ASD.

H. Drs. Baccarelli, Cabrera And Hollander Offer Opinions On Analogy And Experiment That Are Illogical.

Analogy. This "factor requires 'substantiation of relationships similar to the putative causal relationship.'" *Mirena II*, 341 F. Supp. 3d at 249 (citation omitted). Dr. Baccarelli acknowledges that "[p]lacing too much weight on this factor would promote spurious associations as causal—because sometimes analogous drugs do not have analogous effects—and would also ignore truly causal association when [there was] no analogy." (Baccarelli Am. Rep. at 170.) He and Dr. Cabrera nonetheless analogize acetaminophen to valproic acid, which they claim "has been shown to increase oxidative stress and deplete glutathione levels . . . one of the mechanisms by which Depakote is believed to cause NDDs." (*Id.* at 167-68; *see also* Cabrera Am. Rep. at 193.) Plaintiffs' experts do not, however, point to any scientific evidence suggesting that valproic acid—a prescription drug indicated for the treatment of epilepsy, manic episodes associated with bipolar disorder, and prophylaxis of migraine headaches (*see* Pinto-Martin Rep. at 35)—is chemically similar to acetaminophen or shares any characteristics with acetaminophen. (Baccarelli Am. Rep. at 167-68.) Nor does Dr. Cabrera provide any scientific basis for analogizing acetaminophen to even further afield substances like 9-THC from cannabis and mercury. (Cabrera Am. Rep. at 193.) This fundamental failure renders plaintiffs' experts' "analogy" opinions unreliable and inadmissible. *See McClain*, 401 F.3d at 1246 (reversing admission of expert who "failed to show that the PPA analogy is valid or that the differences in chemical structure between PPA and ephedrine make no difference").

Experiment. "This factor focuses on what has been learned from experimentation:

'[c]ausation is more likely if removing the exposure in a population results in a decrease in the occurrence of disease or harm.'" *Davis*, 2019 WL 3532179, at *42 (quoting *Mirena II*, 341 F. Supp. 3d at 242). Plaintiffs' experts agree that randomized clinical trials—the primary type of experimental evidence—have not been conducted on acetaminophen and ASD. (*See* Baccarelli Am. Rep. at 167; Cabrera Am. Rep. at 193.) To the extent plaintiffs' experts state that there is experimental evidence supporting causation (i.e., animal and in vitro studies), they are wrong for all the reasons set forth *infra* and in defendants' Biological Plausibility Brief.

* * *

In sum, even if a Bradford Hill analysis were appropriate, the approaches taken by Drs. Baccarelli, Cabrera and Hollander are unreliable at virtually every step. For this reason, too, their causation opinions should be excluded under *Daubert*.

III. ANIMAL STUDIES CANNOT FILL THE VOID IN THE EPIDEMIOLOGICAL LITERATURE.

Finally, Drs. Pearson and Cabrera's opinions that various studies measuring the purported impact of acetaminophen on animal behavior somehow support a causal relationship are fundamentally unreliable. "[L]aboratory animal studies are generally viewed with more suspicion than epidemiological studies, because they require making the assumption that chemicals behave similarly in different species." *Daniels-Feasel*, 2021 WL 4037820, at *13 (citation omitted). "Accordingly, expert opinions relying on animal studies may only be admitted where 'the gap between what [they] reasonably imply and more definitive scientific proof of causality is not too great,' and the 'inferences are of a kind that physicians and scientists reasonably make from good but inconclusive science.'" *Id.* at *14 (citation omitted).[143]

[143] *See also, e.g.*, *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144-46 (1997) ("far-removed animal studies" did not provide a reliable basis for causation opinions); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F.

As Judge Swain explained in *Daniels-Feasel*, this standard is virtually impossible to meet in the case of ASD. In *Daniels-Feasel*, one of the experts sought to opine that maternal use of Lexapro, an SSRI medication, increased children's risk of developing ASD, "rel[ying] primarily on animal data, despite the significant differences between animals and humans." *Id.* at *16. According to the court, the expert's reliance on animal studies was "particularly concerning" because, as the expert herself conceded, "animals cannot even be diagnosed with autism in the same way humans can," since "'human brains are different than rodent brains,' and animals 'are not communicative in the way . . . humans are.'" *Id.* (citation omitted). Further, the expert did not "discuss other relevant animal studies that constitute contrary authority"—i.e., those that purported to show no cognitive deficits in rats. *Id.* Such a "propensity to cherry-pick data that support[ed] [the expert's] conclusions and disregard contrary data that [were] highly relevant to her conclusions render[ed] her opinion unreliable." *Id.* As detailed below, Drs. Pearson and Cabrera's opinions suffer from the same methodological defects.

First, neither expert articulates a reliable basis for extrapolating from the animal data on which they rely to the diagnosis of ASD in humans. Most fundamentally, Dr. Cabrera admitted that the behavioral indicators for ASD in humans are "different" from what is observed in animals (*see* Cabrera Dep. 196:15-24), which is why animals cannot be diagnosed with ASD (*see id.* 191:15-21; *see also* Cabrera Am. Rep. at 13 (animal data ranks "second from the bottom" on the "hierarchy of evidence")). According to Dr. Cabrera, one cannot "assume that what happens

Supp. 3d 466, 479-81 (E.D. Pa. 2014) ("The [c]ourt notes that in vitro and in vivo animal research is useful for generating hypotheses about human causation, but each hypothesis must be tested and scientifically verified before it can form the basis for a conclusion about causation."); *In re Zantac*, 2022 WL 17480906, at *164 (excluding experts who "have not reliably accounted for species extrapolation because they failed to explain a valid scientific connection between the animal species tested and humans and they made contradictory statements regarding the similarities between rodent metabolisms and human metabolisms"); *In re "Agent Orange" Prod. Liab. Litig.*, 611 F. Supp. 1223, 1241 (E.D.N.Y. 1985) (reliance on animal studies is "not persuasive in this lawsuit" because chemicals behave differently across species), *aff'd*, 818 F.2d 187 (2d Cir. 1987).

in an animal is going to happen in a human or vice versa." (Cabrera Dep. 197:16-198:2.) Dr. Pearson similarly acknowledged that "[r]ats and mice do not have a spoken language that is as complex as humans do" (Dep. of Brandon Pearson ("Pearson Dep.") 120:3-5, Aug. 11, 2023 (Ex. 17)), and emphasized that "rodents aren't little humans" (*id.* 116:25-117:1; *see also* Pearson Rep. at 38 (noting limitations of rodent models of ASD)).

Drs. Cabrera and Pearson nevertheless insist that studies attempting to measure amorphous and disparate behaviors in animals "support the conclusion that [acetaminophen] can cause adverse neurodevelopmental outcomes, including ASD and ADHD, in humans." (Pearson Rep. at 4; Cabrera Am. Rep. at 126.) But Dr. Pearson admitted during his deposition that he was unfamiliar with what the DSM-5 requires for a clinical ASD diagnosis in a human being (despite mentioning the criteria in his report). (Pearson Dep. 68:18-71:7.) In fact, a clinical ASD diagnosis requires persistent deficits in three specific symptom domains, as shown by such behaviors as inability to carry a conversation, abnormalities in eye-contact or lack of facial expressions, or difficulties in sharing imaginative play.[144] These quintessential human behaviors described in the DSM-5 cannot be assessed in animal studies. (*See* Pearson Rep. at 40-43.) Instead, the studies touted by Drs. Cabrera and Pearson cover far-ranging, disparate behaviors entirely untethered to an ASD diagnosis.

For example, both experts cite Hay-Schmidt 2017, which examined whether "APAP alters male rat brains and sexual behavior in adulthood." (*See* Cabrera Am. Rep. at 85; *see also* Pearson Rep. at 106-07.) Other studies similarly focus on outcomes that are not diagnostic of, or specific to, ASD. (*See* Pearson Dep. 67:7-24 (acknowledging that anxiety is not a "diagnostic criteri[on]" for ASD).) And for those metrics that may theoretically track ASD behaviors (e.g.,

[144] *See* DSM-5 at 50 (Criteria A.1., A.2., A.3).

social behavior), Dr. Cabrera candidly admitted that researchers are essentially guessing whether observed animal behavior is pro-social, anti-social or neutral. (*See* Cabrera Dep. 195:22-24 (testifying that researcher interpretation of observed animal conduct "is certainly open as far as what that means and how we interpret their behaviors").) Moreover, a number of the studies cited by Dr. Cabrera as providing "'clear evidence' that ***perinatal*** APAP exposure" results in ASD (Cabrera Am. Rep. at 126-27 (emphasis added)) are even further afield because they did not test in utero or perinatal exposure. For example, Ishida 2007, Gould 2012 and Zhao 2017 all dosed ***adult*** mice or rats with acetaminophen.[145] Plaintiffs' own expert, Dr. Pearson, appears to agree that such studies are irrelevant, having excluded Ishida 2007 on the stated ground that the "study was in 5-week-old mice which is the equivalen[t] of late adolescen[ce] or early adulthood in humans." (Pearson Rep. at 70; *see also* Rebuttal Rep. of Brandon Pearson ("Pearson Rebuttal Rep.") at 5, July 28, 2023 (Ex. 18) (noting that studies "where APAP was administered to adult rodents . . . [b]y their very nature . . . take place outside the context of the neurodevelopmental processes").) And, as Dr. Cabrera conceded at his deposition, "studies . . . examining effects on adult mice . . . may be informative on concentrations or mechanism, but they're not going to be necessarily informative on the outcome, the specific ASD or ADHD outcome." (Cabrera Dep. 199:25-200:8.)

Second, Drs. Cabrera and Pearson "cherry-pick [the] data" from animal studies, ignoring findings that undermine their conclusions. *Daniels-Feasel*, 2021 WL 4037820, at *16. For example, both experts rely on Klein 2020, with Dr. Cabrera stating that it constitutes "clear

[145] *See* Ishida, *Effect of Acetaminophen, a Cyclooxygenase Inhibitor, on Morris Water Maze Task Performance in Mice*, 21(7) J. Psychopharmacol. 757 (2007); Gould, *Acetaminophen Differentially Enhances Social Behavior and Cortical Cannabinoid Levels in Inbred Mice*, 38 Prog. Neuro-Psychopharmacol. Biol. Psychiatry 260 (2012) ("Gould 2012"); Zhao, *Acetaminophen Attenuates Lipopolysaccharide-Induced Cognitive Impairment Through Antioxidant Activity*, 14(17) J. Neuroinflammation 1 (2017).

evidence" that prenatal acetaminophen impairs "learning or social behavior" based on "impaired nest seeking behavior" and "decreased rostral grooming."[146] (Cabrera Am. Rep. at 126-27; *see also* Pearson Rep. at 94.) But Dr. Pearson does not acknowledge that the rodents "did not present altered social behavior in the three-chamber test."[147] Indeed, the researchers observed that "exposure did not affect time in the social area . . . social preference in relation to a new object . . . or time sniffing the co-specific."[148] And to the extent Dr. Cabrera does mention these unfavorable findings in his report, he does not explain whether they can be reconciled with his conclusions (and, if so, how).

Likewise, Dr. Cabrera relies on Harshaw & Warner 2022, in which mice exposed to fever and acetaminophen demonstrated shifts in repetitive behavior and increased social caution as "clear evidence of impaired social-emotional and repetitive behaviors." (Cabrera Am. Rep. at 127.) But nowhere does Dr. Cabrera mention (much less grapple with) the authors' finding of no significant effect in marble burying behavior for mice exposed to acetaminophen,[149] a supposedly critical measure of ASD behavior according to Dr. Pearson.[150] Similarly, while Dr. Cabrera cites Gould 2012 as "clear evidence" supporting his opinion that "APAP exposure is

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146 Dr. Pearson's reliance on "decreased" rostral grooming is illogical in light of his recognition that "[t]he duration and bouts of grooming are measures of repetitive behavior" (i.e., a symptom of ASD). (Pearson Rep. at 43.) In other words, to the extent there could ever be an animal model of ASD, it would be expected to show ***increased*** grooming as a repetitive behavior, which is exactly what mice with mutations of "particular genes associated with [ASD]" demonstrate. *See* Kalueff, *Neurobiology of Rodent Self-Grooming and its Value for Translational Neuroscience*, 17(1) Nat. Rev. Neurosci. 45, at Table 1 (2016).

147 Klein, *Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny*, 77 Neurotoxicol. Teratol. 1, 5 (2020).

148 *Id.*

149 *See* Harshaw & Warner, *Interleukin-1β-Induced Inflammation and Acetaminophen During Infancy: Distinct and Interactive Effects on Social-Emotional and Repetitive Behavior in C57BL/6J Mice*, 220 Pharmacol. Biochem. Behav. 1, 5 (2022).

150 *See* Pearson Rep. at 42 ("The number of marbles buried are used to represent repetitive, compulsive-like behavior in rodents (ASD factor III).").

reported to impair learning or social behavior" (Cabrera Am. Rep. at 126),[151] he ignores that the study actually found that "[a]cetaminophen administration ***enhanced*** social behavior in adult male mice with otherwise inherently low sociability."[152] And a number of the rodent studies cited by Dr. Pearson found no significant association or even found beneficial effects in key symptom domains such as communicative behaviors.[153]

The only expert who attempts to justify his cherry-picking is Dr. Pearson, who asserts that even animal study "findings that are in the opposite direction of the prediction nevertheless demonstrate that the sensitive neurobehavioral system is perturbed by the developmental exposure to the medication" and that "[a] directional concordance is not required." (Pearson Rebuttal Rep. at 4.) But Dr. Pearson's justification directly contradicts his own report, which enumerates the expected results in animal studies that are theorized to correlate with ASD symptoms. (Pearson Rep. at 29-34.) It is also illogical. If one were to accept Dr. Pearson's justification at face value, it would mean that results showing that exposed mice have fewer instances of self-grooming (i.e., ***decreased*** repetitive behaviors) are evidence of a causal relationship with ASD in humans. Such an approach to animal studies is unscientific and leaves no doubt that Dr. Pearson's opinions were made for litigation.

IV. DRS. BACCARELLI AND LOUIE'S OPINIONS SHOULD BE EXCLUDED FOR ADDITIONAL REASONS.

A. Dr. Baccarelli's "Navigation Guide" Opinion Is Similarly Unreliable.

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151 Once again, Dr. Cabrera fails to explain how an experiment that involved giving APAP to adult mice is an adequate proxy for prenatal APAP use in humans.

152 Gould 2012, *supra* note 145, at 268 (emphasis added).

153 *See, e.g.*, Rigobello, *Perinatal Exposure to Paracetamol: Dose and Sex-Dependent Effects in Behaviour and Brain's Oxidative Stress Markers in Progeny*, 408 Behav. Brain Res. 1 (2021) (no significant effect of acetaminophen use on sociability index, time spent in social areas, or time spent sniffing other animals); Suda, *Therapeutic Doses of Acetaminophen with Co-Administration of Cysteine and Mannitol During Early Development Result in Long Term Behavioral Changes in Laboratory Rats*, 16(6) PLoS ONE 1 (2021) (finding no effect on play or grooming behaviors—two common metrics hypothesized to relate to social abilities).

Dr. Baccarelli also purports to apply the "Navigation Guide" method (*see* Baccarelli Am. Rep. at 13-23), which "was recommended by the Committee to Review EPA's Toxic Substances Control Act as an approach the EPA should use in evaluating TCPA [sic] risks." (*Id.* at 12-13 (citing National Academies of Sciences, Engineering, and Medicine (2021), *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*).) There are several fundamental problems with this analysis.

As a threshold matter, the Navigation Guide was developed as a regulatory tool and is thus aimed not at proving causation but at identifying potential risks, an approach that "employs a ***lower standard*** than a scientific causation approach requires." *In re Zicam Cold Remedy Mktg., Sales Pracs., & Prods. Liab. Litig.*, No. 09-2096, 2011 WL 798898, at *11 (D. Ariz. Feb. 24, 2011) (emphasis added); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 387 F. Supp. 3d 323, 356 (S.D.N.Y. 2019) (citation omitted) (noting that regulators use a "different standard than a court does to evaluate evidence of causation in a products liability action"), *aff'd*, 982 F.3d 113 (2d Cir. 2020). In any event, the one U.S. regulator with oversight over the safety of acetaminophen (i.e., the FDA) has repeatedly studied and rejected the notion that the medication is capable of causing either ASD or ADHD in children, or that any precautionary approach is needed. The Navigation Guide cannot substitute for actual agency review.

In any event, Dr. Baccarelli did not apply this approach in a methodological manner. The "Navigation Guide" calls for a "systematic review" of the scientific evidence through four steps: (1) specifying the study question; (2) selecting the evidence; (3) rating the quality and strength of the evidence, culminating in "one of five possible statements" (i.e., "known to be toxic," "probably toxic," "possibly toxic," "not classifiable," or "probably not toxic"); and (4) grading

the strength of the recommendations.[154] Dr. Baccarelli did not perform these steps reliably. To the contrary, his entire review of the evidence was results-oriented because he "cherry-pick[ed] from the 'scientific landscape,'" highlighting limited epidemiological findings that support his opinions and disregarding those that undermine his conclusions. *See Daniels-Feasel*, 2021 WL 4037820, at *5. In other words, he did not select evidence, rate the evidence or grade the strength of the recommendations in a scientific manner.

In addition, despite acknowledging that the Navigation Guide analysis is intended to be performed by teams in order to minimize bias (*see* Baccarelli Dep. 317:18-318:4), Dr. Baccarelli undertook his analysis individually (*see id.* 333:20-335:5), which is particularly problematic given the obvious potential for bias in this circumstance.

B. Dr. Baccarelli's Litigation Opinions Are Separately Inadmissible Because They Contradict His Own Prior Published Opinions.

Dr. Baccarelli's causation opinions should also be excluded because they directly contradict the views he published about acetaminophen and ASD prior to becoming an expert for plaintiffs. This is a strong indication that Dr. Baccarelli has not "employ[ed] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999); *see also Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007) (courts should carefully scrutinize experts whose "opinions were conceived, executed, and invented solely in the context of . . . litigation") (citation omitted). Indeed, courts are especially skeptical of experts who adopt litigation opinions that contradict their prior published views. *See, e.g.*, *In re Fosamax Prods. Liab. Litig.*, No. 1:06-md-1789 (JFK), 2009 WL 2878439, at *5 (S.D.N.Y. Sept. 9, 2009) (excluding opinion

[154] Woodruff & Sutton, *The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes*, 122(10) Environ. Health Perspect. 1007, 1008 (2014).

of general causation expert that was contrary to his academic publications; reversal of expert's opinion "raises a question as to whether it was made independent of litigation concerns"); *Zoloft*, 26 F. Supp. 3d at 460 (excluding opinion that SSRIs as a class have teratogenic effects because it "is directly contrary to the findings of her own peer-reviewed, published research"); *Fireman's Fund Ins. Co. v. Canon U.S.A., Inc.*, 394 F.3d 1054, 1059 (8th Cir. 2005) (noting that a "sudden reversal of opinion . . . seriously undermines the reliability of" an expert's opinion).

Dr. Baccarelli's opinions in this litigation are diametrically opposed to what he has written in the peer-reviewed literature. Most notably, in Laue 2019, Dr. Baccarelli reported that the results of meconium samples "do not support prior reports of adverse neurodevelopmental effects of *in utero* exposure to acetaminophen,"[155] a finding Dr. Baccarelli found so compelling that he publicized it on Twitter in 2020 and took to Twitter once again to emphatically reject Dr. Bauer's critique of Laue. And as recently as 2022, Dr. Baccarelli again co-authored a paper that said "more studies in a diverse range of cohorts are needed before suggesting a change in clinical practice" regarding acetaminophen use for pregnant women.[156]

The thrust of Dr. Baccarelli's causation opinions and overall approach to the underlying data on acetaminophen and ASD are directly at odds with these prior published statements and findings, with Dr. Baccarelli going so far as to criticize his "own paper" for ***its*** criticisms of studies on which he now seeks to rely, as well as its overall conclusion essentially finding no association between acetaminophen and adverse neurodevelopmental outcomes. (*See* Baccarelli Dep. 276:1-4; *see also* Baccarelli Am. Rep. at 106 (relying on Liew 2016, which measured "IQ in 5-year-olds"—i.e., the same outcome that Dr. Baccarelli rejected as a proxy for ASD in

155 Laue 2019, *supra* note 65, at 138.

156 Baker 2022, *supra* note 68, at 6.

Laue).) Dr. Baccarelli's proffered justification was that he was simply "wrong" and that he wishes he could "take a time machine" and change his prior positions. (*See* Baccarelli Dep. 282:8-13, 283:16-23.) But that is not a credible explanation. Rather, the only conceivable explanation for this about-face is that he is now being paid by plaintiffs, which "raises a question as to whether [his opinions were] made independent of litigation concerns" (i.e., in the laboratory rather than in the courtroom). *In re Fosamax*, 2009 WL 2878439, at *5.

C. Dr. Louie's Increased-Risk Opinions Are Unreliable.

Dr. Louie primarily opines that exposure to acetaminophen for a cumulative period of 28 days "increases the risk of ASD/ADHD development by two-fold as compared to [children] with no exposure to acetaminophen." (Louie Am. Rep. ¶ 28.) In so opining, Dr. Louie does not identify when during the gestational period such a cumulative 28-day period suffices to increase the risk of developing ASD. Thus, according to Dr. Louie, it makes no difference whether the cumulative exposure occurs during the first month of the pregnancy or the last month. (*See* Louie Dep. 90:7-15). As discussed in connection with plaintiffs' experts' epidemiology-based opinions, such an incoherent and loose approach to causation is unscientific and unreliable.

Although Dr. Louie asserts that "studies by Brandlistuen et al[.], Ystrom et al[.], and Gustavson et al[.] all found that acetaminophen exposure beyond 28 days showed a two-fold increased risk for childhood ADHD and ASD diagnosis" (Louie Am. Rep. ¶ 81), none of those studies involved ASD diagnoses. Rather, Brandlistuen (to which Dr. Louie "assigned the greatest weight") (Louie Am. Rep. ¶ 71) evaluated "psychomotor development," "behavior" and "temperament,"[157] while Ystrom 2017 and Gustavson 2021 addressed ADHD diagnoses.[158]

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157 Brandlistuen 2013, *supra* note 71.

158 *See, e.g.*, Ystrom 2017, *supra* note 72; Gustavson 2021, *supra* note 72.

Accordingly, Dr. Louie "misrepresent[s] the underlying epidemiological data that [he] claims supports [his] opinion." *Daniels-Feasel*, 2021 WL 4037820, at *17. This is fatal to his opinion because, as previously discussed, studies of behavioral outcomes and ADHD diagnoses are not reliable proxies for clinical ASD diagnoses.

Moreover, the three studies do not even support the notion that exposure to acetaminophen for a cumulative period of 28 days increases the risk of other neuro-developmental outcomes. Although Brandlistuen reported an increased risk of certain behavioral outcomes (e.g., poorer gross motor development and communication) among children whose mothers took acetaminophen for more than 28 days, the authors cautioned that "because clinical assessments with diagnostic tools were not available in this study, we could not determine the clinical importance of the difference observed."[159] The authors also found that some of the most relevant symptom domains for ASD (e.g., "sociability," "shyness" and "internalizing problems") were not significantly associated with acetaminophen use for any number of days.[160] In any event, Brandlistuen simply divided usage into 1-27 days and 28+ days, with the latter category encompassing mothers who took the medication for anywhere from 29 days to the full nine months of their pregnancies. Ystrom 2017 and Gustavson 2021 found an increased risk of ADHD with 29+ days of use, but similarly lumped women with widely varying exposures together in the 29+ days category.[161] None of these studies, which broadly aggregate women who took acetaminophen anywhere from one to nine months of pregnancy, can support a finding that 28 or 29 days of exposure to acetaminophen is the level of exposure at which the medication

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159 Brandlistuen 2013, *supra* note 71, at 1709, 1711.

160 *Id.* at 1709 (Table 4); *see also* Vlenterie 2016, *supra* note 131, at 2004 (finding no significant increase in risk of eight out of ten behavioral outcomes for greater than 28 days of use).

161 *See, e.g.*, Ystrom 2017, *supra* note 72; Gustavson 2021, *supra* note 72.

is supposedly capable of causing harm (much less increasing the risk of harm two-fold).

Dr. Louie also asserts that "[f]indings from the Liew studies published in 2014 and 2016, and the Vlenterie study, have results that are generally consistent with the [28-days] exposure threshold." (Louie Am. Rep. ¶ 81.) But only one of those studies—Liew 2016—looked at ASD diagnoses, and it "count[ed] total weeks of use," not days of use.[162] In other words, the authors had no idea whether a woman who reported six weeks of use took acetaminophen every day for those six weeks or once a week for those six weeks. Moreover, as Dr. Louie acknowledges, Liew 2016 reported an adjusted hazard ratio of 1.23 for 2-5 weeks of acetaminophen use (Louie Am. Rep. ¶ 78), which clearly does not support Dr. Louie's opinion that exposure to the medication for any period is capable of increasing the risk of ASD "by two-fold."[163] And although Vlenterie 2016 reported a statistically significant increased risk for delayed attainment of motor milestones, the authors did not report any significantly increased risk for the ***nine*** other behavioral outcomes, including communication ability, emotionality, activity, sociability, and shyness, as the authors expressly noted. Accordingly, Dr. Louie's opinion "'is connected to existing data only by the *ipse dixit* of the expert[,]' [which] is not reliable." *Daniels-Feasel*, 2021 WL 4037820, at *20 (quoting *Joiner*, 522 U.S. at 146).[164]

Finally, Dr. Louie's fallback opinion—that a cumulative dose over pregnancy, ranging from 18,200 mg to 112,000 mg increases the risk of developing ASD—is similarly unreliable.

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[162] Liew 2016, *supra* note 25, at 956.

[163] Dr. Louie's reliance on Liew 2014 and Vlenterie 2016 is similarly misplaced. Liew 2014 used the same cohort and data collection methods from Liew 2016 in examining ADHD diagnoses. *See* Liew, *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*, 168(4) JAMA Pediatrics 313, 314-15 (2014) (Liew 2014 examined Danish National Birth Cohort and reported on weeks of use); *see* Vlenterie 2016, *supra* note 131, at 2003.

[164] Dr. Baccarelli also opines in passing that based on the "literature," "generally 28 days or more of prenatal acetaminophen use is sufficient to generate a statistically significant increase in risk of signs and symptoms of ASD." (Baccarelli Am. Rep. at 172-73.) But the only "literature" Dr. Baccarelli cites in support—Brandlistuen and Liew 2016—either does not support the 28-day theory or actually undercuts it, as discussed above.

(*See* Louie Am. Rep. ¶¶ 26-31, 188-89; *see also* Louie Dep. 100-01.) When asked to identify scientific support for this opinion, Dr. Louie pointed to two studies—Ystrom 2017 and Liew 2016 (Louie Dep. 102:22-103:10)—but neither substantiates his claim. Putting aside that Ystrom 2017 involved an ADHD (not ASD) diagnosis, the authors found that use of acetaminophen for fewer than eight days was ***negatively*** associated with that condition, undermining Dr. Louie's opinion.[165] And although Liew 2016 did look at ASD diagnoses, the authors did not report any data on dosage or how many days within a given week the mother used acetaminophen. In any event, as previously noted, Liew 2016 found that risks for ASD diagnoses ***decreased*** as weeks of use increased from 2-5 weeks to 6-20 weeks, undercutting Dr. Louie's conclusion.[166] Accordingly, Liew 2016 does not support Dr. Louie's fallback opinion.

In short, while Dr. Louie's 28-day threshold opinion may appear at first glance to be more nuanced than the opinions of plaintiffs' other experts, it is essentially pulled from thin air. Needless to say, that is not a proper methodology under *Daubert.* For this reason, too, Dr. Louie's opinions are inadmissible under *Daubert.*

CONCLUSION

For the foregoing reasons, the Court should exclude the opinions of Drs. Baccarelli, Cabrera, Hollander, Louie and Pearson that maternal acetaminophen use during pregnancy can cause ASD in children.

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Respectfully submitted,

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165 Ystrom 2017, *supra* note 72, at 6 (Table 2).

166 *See* Liew 2016, *supra* note 25, at 955 (Table 2).

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